THE DESIGN AND SYNTHESIS OF POTENTIAL INHIBITORS OF FUCOSYLTRANSFERASES

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Dedicated to my family

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CONTENTS

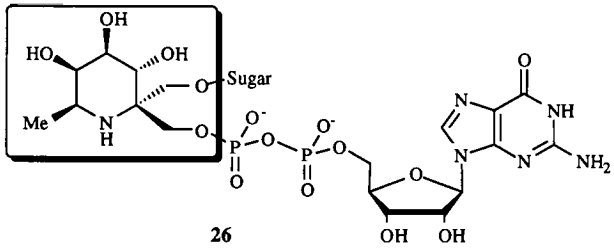
ABBREVIATIONS

Ac	acetyl
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
BTAC	benzyltrimethylammonium chloride
*t*Bu	*tert*-butyl
Bz	benzoyl
C.I.	chemical ionisation
COSY	Correlation Spectroscopy
DCM	dichloromethane
DFJ	deoxyfuconojirimycin
DIBAL	di-*iso*-butylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMJ	deoxymannojirimycin
2,2-DMP	2,2-dimethoxypropane
DNJ	deoxynojirimycin
E.I.	electron impact
F.A.B	fast atom bombarbment
FucT	fucosyltransferase
IBX	o-iodoxybenzoic acid
J	coupling constant
m/z	mass/charge ratio
mp	melting point
NMO	*N*-methyl-morpholine-*N*-oxide
nOe	nuclear Overhauser enhancement
nmr	nuclear magnetic resonance

Ph	phenyl
R_F	refractive index
sLe^x	sialyl Lewis-X
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	tetramethylpiperidinyl-1-oxy
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)
Z	benzyloxycarbonyl

ABSTRACT

This thesis describes the design and synthetic approach to a potential transition state inhibitor **26** of an α(1,3)-fucosyltransferase - an important enzyme involved in the inflammatory response where white blood cells are recruited to the site of injury.



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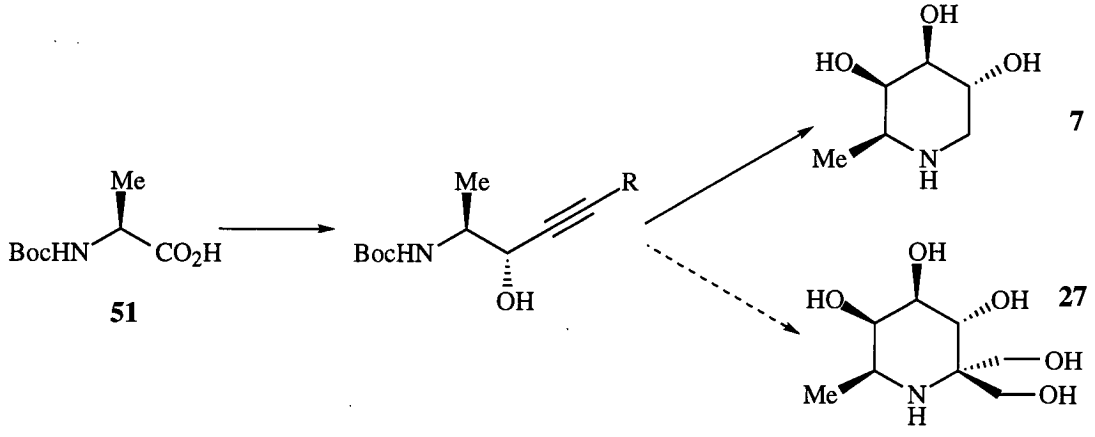
Chapter 1 reviews the literature of potential inhibitors of both glycosyltransferases and glycosidases and outlines the aim of the project. Chapter 2 reveals the retrosynthetic strategy adopted for the trisubstrate analogue **26** and of the core azasugar portion which is a *bis*-hydroxymethylpiperidine **27**. The synthetic challenge in this project resided in the synthesis of this unit and initially, an asymmetric synthesis of the known azasugar L-deoxyfuconojirimycin (DFJ) **7**, which contains four of the required stereogenic centres of the core azasugar **27** was investigated. Chapter 3 describes the sucessful synthesis of **7** in 14 steps commencing from the readily available amino acid *N*-Boc-L-alanine **51**.



It was envisaged that the route to DFJ could subsequently be elaborated to the *bis*-hydroxymethylpiperidine **27**, but due to unforeseen problems a revised approach to the prime target from *N*-Boc-L-alanine **51** was adopted. Chapter 4 outlines 10 steps that have been completed *en route* to an appropriately functionalised acyclic system which is anticipated to undergo a Lewis acid catalysed *6-exo-tet* cyclisation of an amine function onto a gem-disubstituted epoxide to furnish a cyclised precursor to the target azasugar **27**.

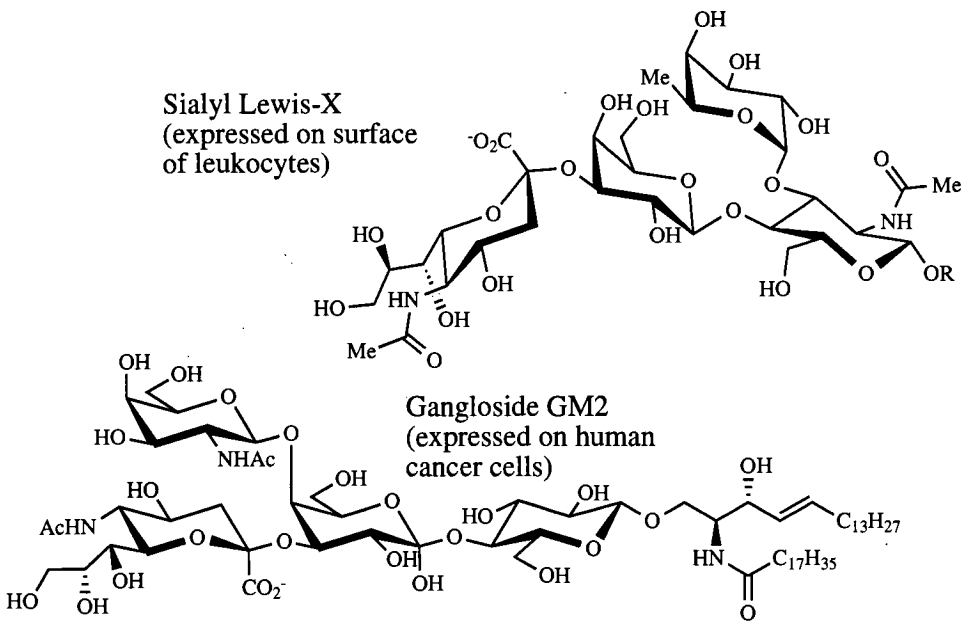
1. INTRODUCTION

1.1 GLYCOBIOLOGY:- THE ROLE OF CARBOHYDRATES IN BIOLOGICAL PROCESSES

Carbohydrates are very important compounds in a wide range of biological processes and the emerging field of glycobiology is enabling an understanding of the interactions and mechanisms involved in the many different processes of the complex carbohydrates which are present on cell surfaces. The majority of carbohydrates of biological relevance are attached to proteins or lipids and can be highly branched molecules connected by many different linkages. These protein or lipid bound carbohydrates are referred to as glycoconjugates and can be classified as glycoproteins, glycolipids and proteoglycans, and differ by their characteristic carbohydrate tethers.

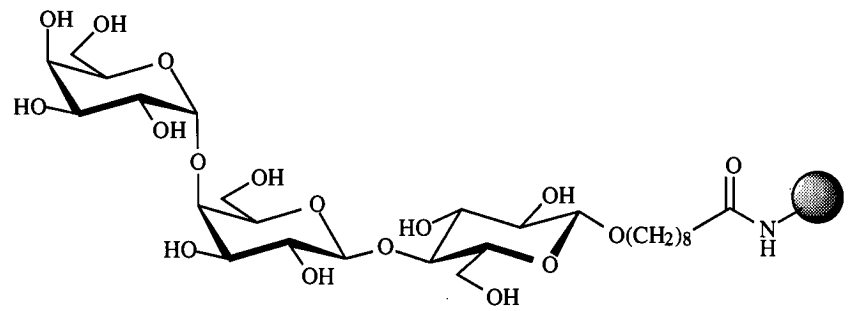
The carbohydrate residues of the glycoprotein and glycolipids act as binding sites for other large molecules such as proteins, bacterial toxins and antibodies. Both are complex glycoconjugates and are fundamental to a wide range of processes including fertilisation, immune defence, viral infection, cell growth, cell-cell adhesion and inflammation. Figure 1 highlights an example of known carbohydrates that are expressed on human cells.[1,2]

Figure 1

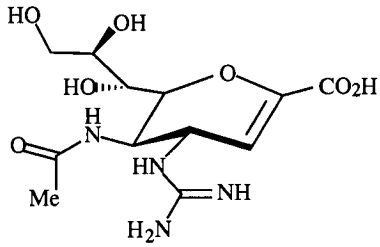


Through the understanding of complex carbohydrate structures a number of carbohydrate based drugs have been developed for a range of therapeutic applications including anti-inflammatories, cancer chemotherapy, diabetes, anti-virals and infectives and also neurological therapies, several of which are shown in Figure 2. Carbohydrates such as sialyl Lewis-X and GM2 have also been synthesised and used as potential drug candidates.[1,2]

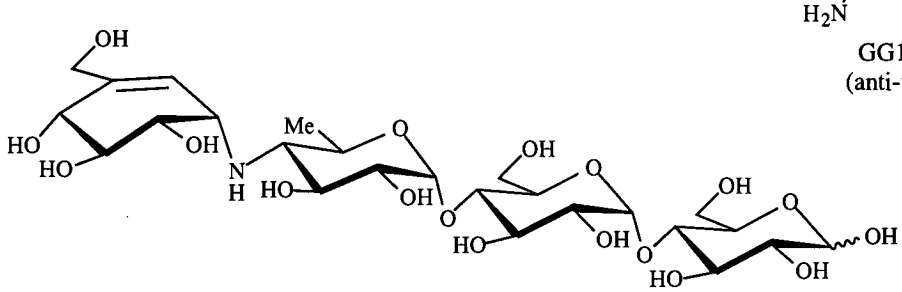
Figure 2



SYNSORB Pk
(anti-infective)



GG167
(anti-viral)



Acarbose
(diabetes)

These carbohydrate drugs exert their potency by either mimicking the cell-bound carbohydrate, thereby blocking the corresponding interaction, or by inhibiting the specific enzymes which create the active carbohydrate hence decreasing or increasing the amount of active compound that is causing the disease state.

The area of interest in this project is the carbohydrate mediated cell-cell adhesion process that occurs as a result of tissue injury or infection.

1.2 Cell-Cell Adhesion And The Inflammatory Response

Carbohydrate mediated cell adhesion is a basic cellular mechanism that is required for many functions including pathogen infectivity and cellular immune responses and has also been implicated in metastasis of tumours.[3]

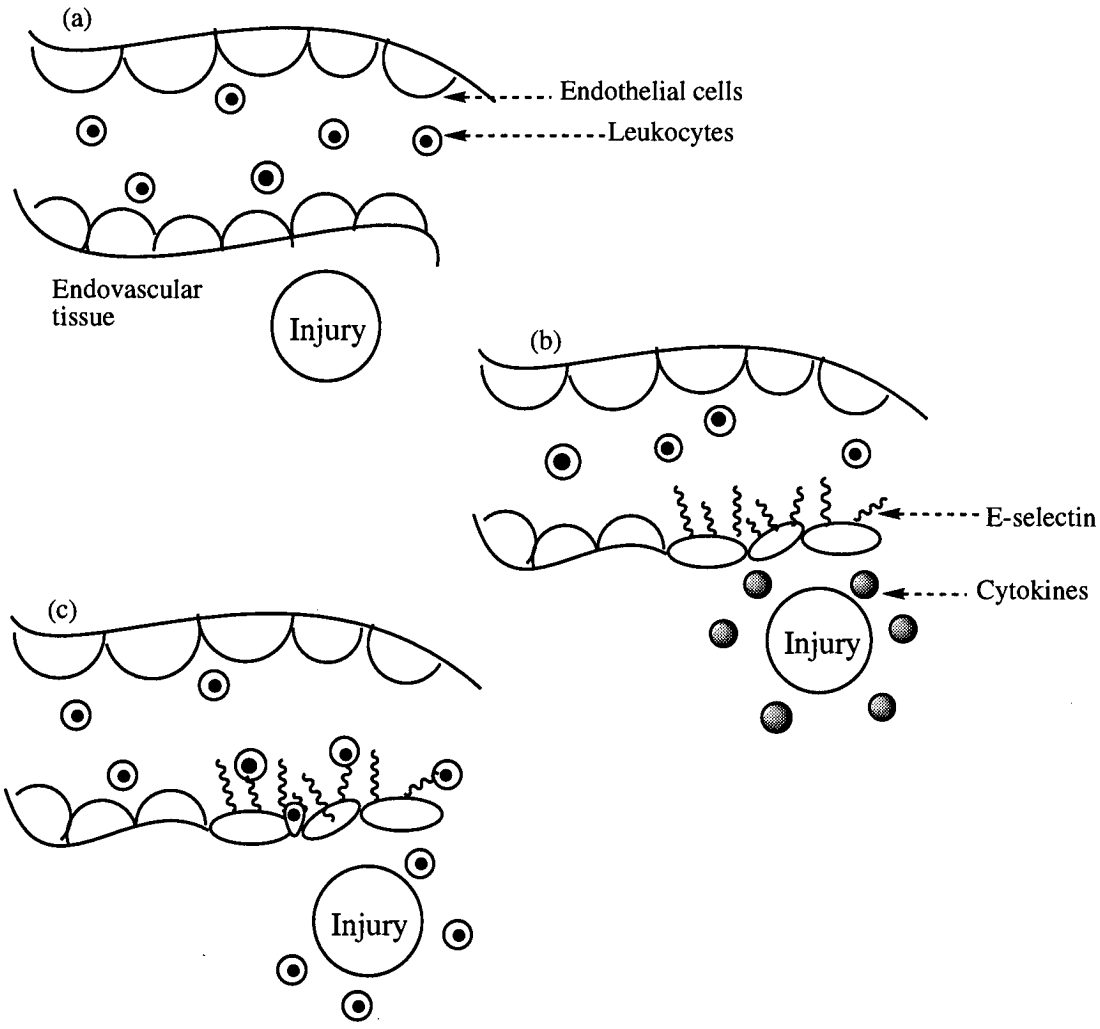
Cells are completely covered with glycocalyx, a layer of carbohydrates arising from glycoproteins, glycolipids or glycosaminoglycans, and as these carbohydrates dominate the exterior of the cell membrane they are in ideal positions to mediate initial contacts between two cells.

The LECCAMS or selectins are a family of cell adhesion molecules which mediate adhesive interactions between circulating leukocytes (white blood cells) and the vascular endothelium. One of the three members of this family is E-selectin (formally known as ELAM-1, endothelium leukocyte adhesion molecule-1) and is displayed on the surface of the endothelial cells when inflammation occurs. It promotes adhesion of neutrophils, monocytes, and a sub-population of lymphocytes (the 3 main types of leukocytes) to the endovascular wall adjacent to the site of inflammation.[4-8]

The recruitment of leukocytes to the injured tissue is illustrated in the simplified diagram shown in Figure 3. When tissue injury occurs (a) small peptides called cytokines are released to signal E-selectin synthesis on the endothelial cells which also change shape (b). The leukocytes then roll along the surface of the endothelial cells *via* protein-protein interactions mediated by proteins called integrins (displayed on the leukocytes) and a protein ligand (on the endothelial cells) called ICAM-1 (intracellular adhesion molecule-1), (c). The leukocytes are then able to squeeze through the gaps between the endothelial cells and enter the adjacent tissue to help repair injury.[9]

Unfortunately, there is a series of acute and chronic diseases which result from the misdirected or excessive migration of too many leukocytes to the area of infection such as cardiogenic shock, stroke, rheumatism, psoriasis and bacterial meningitis. It is also thought that certain cancer cells may exploit this phenomenon of adhesion to spread throughout the body, hence compounds that alter cell-cell interactions may have many potential medical applications as anti-inflammatory, anti-infective and anti-tumour agents.

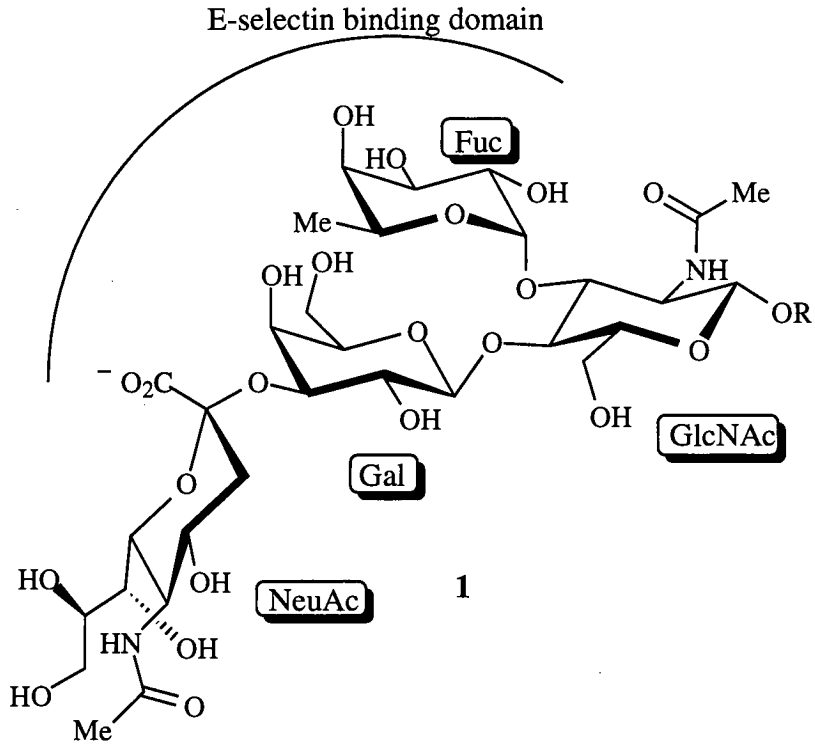
Figure 3



The oligosaccharide which has been found to interact with E-selectin in the above process is a tetrasaccharide called sialyl Lewis-X (sLe^x) **1** and is found at the terminus of glycolipids displayed on the surface of the leukocyte membrane, Figure 4.[4,5,10]

Through a series of inhibition studies using sLe^x and analogues, it was proposed that the interaction between E-selectin and sLe^x was multivalent and the active binding domain of sLe^x arises from the carboxylate of the *N*-acetyl-neuraminic acid (NeuAc), the 4 and 6-hydroxyl groups of the galactose residue and the three hydroxyl groups of the fucose. The methyl group of fucose is not essential, as this residue can be exchanged with arabinose (whereby the methyl is replaced by H).[9,11]

Figure 4



1.2.1 Control of cell-cell adhesion

The development of therapeutic agents for treatment of inflammation related diseases and cancers requires the need to prevent healthy tissue damage, *i.e.* to control the rate of flow of leukocytes through the endothelium wall. Two main approaches to this are as follows:-

1. To synthesise sLe^x and analogues as competitive inhibitors of the binding interaction between the sLe^x-containing leukocytes and E-selectin.

2. To inhibit the glycosyltransferase enzymes that are involved in the biosynthesis of the intracellular sLe^x. One of the enzymes that has been targeted for inhibition is the α(1,3)-fucosyltransferase [α(1,3)-FucT].

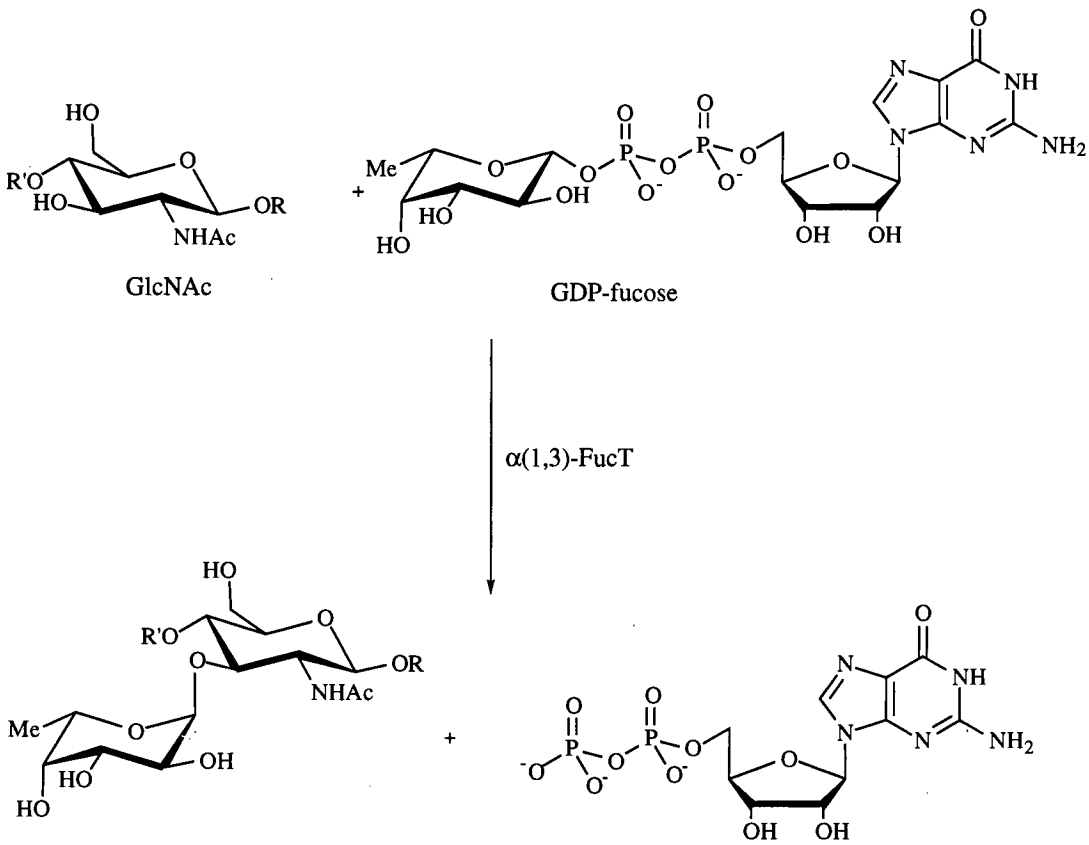
There is literature precedent for the synthesis (both chemical and enzymatic) of sLe^x and analogues as inhibitors,[12-14] but very little information on the inhibition of the fucosyltransferases that catalyse the synthesis of sLe^x[15-17] thereby making this a very interesting target.

1.2.2 The role and mechanism of the α(1,3)-FucT

The two families of enzymes that assemble and shape the carbohydrates of bioactive glycoprotein and glycolipid conjugates are the glycosidases and glycosyltransferases. Glycosidases catalyse the hydrolysis of glycosidic linkages and are involved in the trimming of oligosaccharides. Glycosyltransferases catalyse the transfer of monosaccharides from sugar-nucleotide donors (*e.g.* GDP-fucose) to suitable acceptors resulting in lengthening of oligosaccharides.

The final enzyme involved in the biosynthesis of sLe^x is an α(1,3)-FucT which catalyses the transfer of the L-fucose moiety from guanosine diphosphate β-L-fucose (GDP-fucose) to the 3-OH of *N*-acetyl glucosamine (GlcNAc) resulting in inversion of configuration at the anomeric carbon of the fucose residue (Figure 5). Glycosyltransferases also require metal cofactors, typically calcium or manganese (II) for full activity.

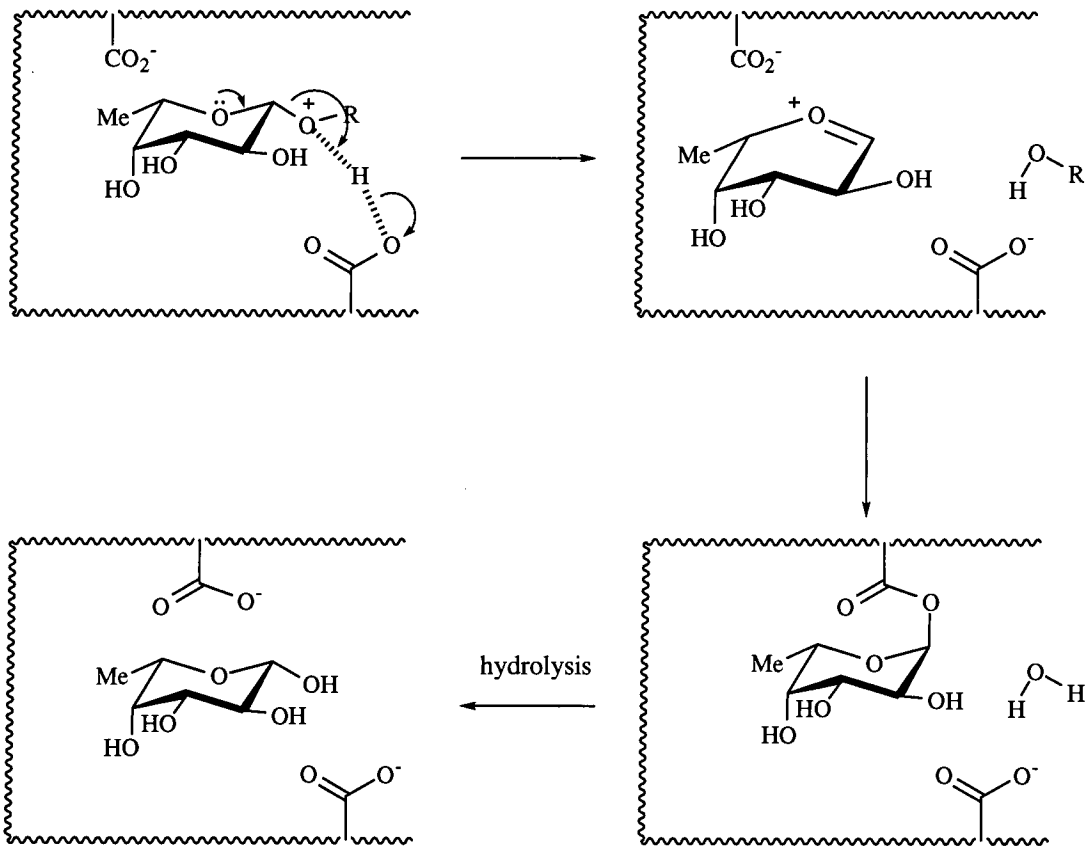
Figure 5



R' = remainder of oligosaccharide

There is little known about the mechanism of glycosyltransferase catalysed reactions. However, it has been proposed that there are similarities with the mechanism of glycosidase catalysed hydrolysis which has been well studied, which can result in inversion or retention of the configuration at the anomeric centre dependent on the enzyme involved.[8-20] The mechanism for enzymes that hydrolyse with retention of configuration (illustrated using fucose as an example in Figure 6) is proposed to go *via* a transient glycosyl cation after department of the R-OH aglycon. This is then stabilised by a carboxylate side chain of the enzyme producing a glycosyl-enzyme intermediate that will then undergo hydrolysis at the active site.

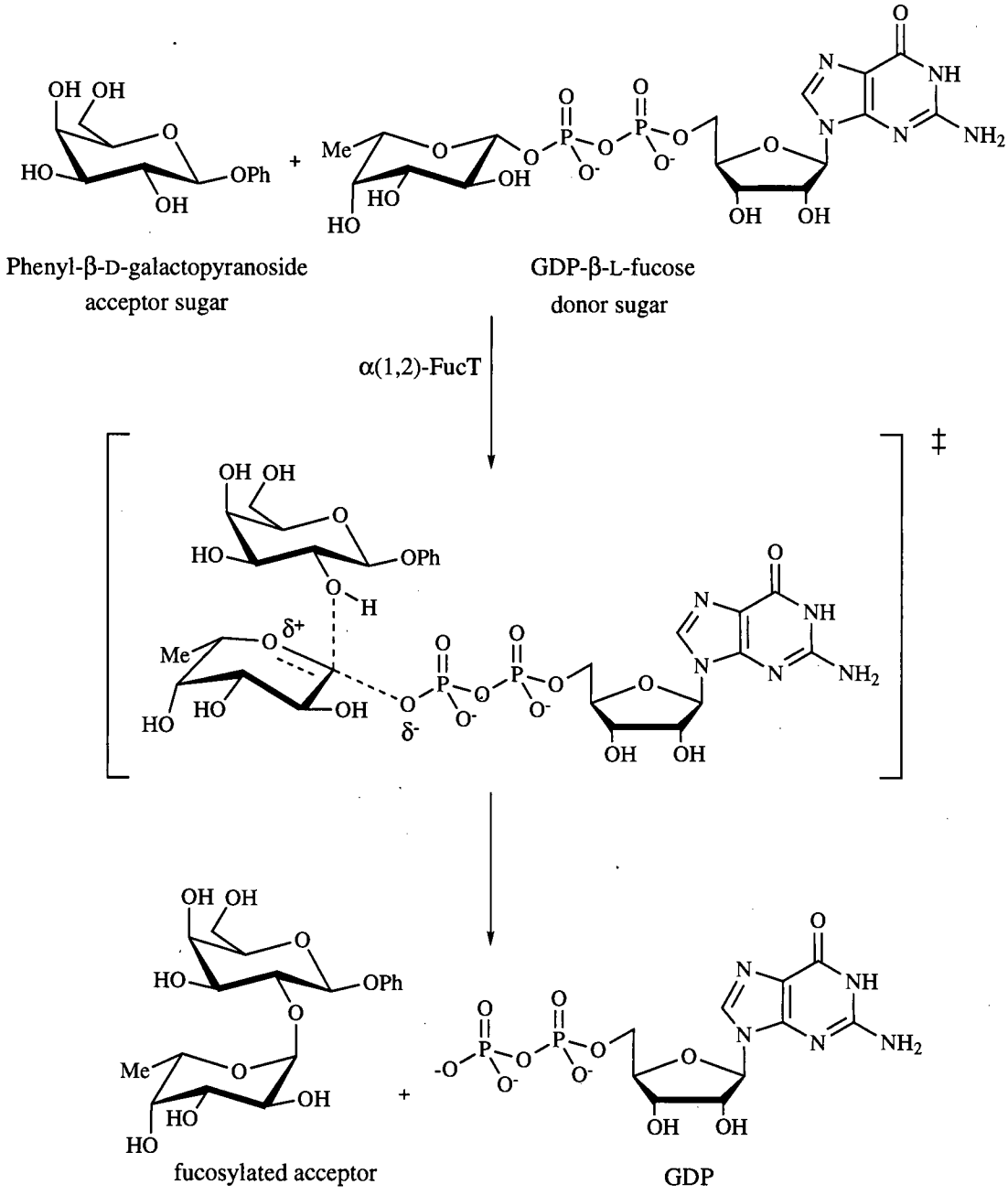
Figure 6



The glycosyltransferase catalysed reaction may proceed through a similar glycosyl cation which then undergoes nucleophilic attack from another sugar residue resulting in the glycosylated product. The divalent metal co-factor *e.g.* manganese (II), which is essential for glycosyltransferase activity is thought to form a 6-membered ring complex with the diphosphate group of the GDP moiety.[17]

Several years ago, Palcic *et al.*,[21] postulated that the enzymatic fucosyl transfer from GDP-fucose to the 2-OH group of β-D-galactopyranoside catalysed by an α(1,2)-FucT, proceeded *via* an ion-pair mechanism involving a flattened half-chair glycosyl cation intermediate (Figure 7). This implies that GDP-fucose and the acceptor sugar are simultaneously interacting with the enzyme in the transition state.

Figure 7



This proposed transition state has been used extensively as a basis in the search for new inhibitors of glycosyltransferases in general, and recently Wong and co-

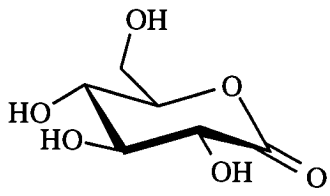
workers[17,22] have studied α(1,3)-FucT-V (one of the 5 human α(1,3)-FucT's that have been cloned to date) and have found that the enzyme has an ordered, sequential mechanism with GDP-fucose binding first and the product GDP released last. Results also suggest that significant glycosidic cleavage of the GDP-fucose bond occurs prior to the nucleophilic attack by the acceptor sugar - an overall process between S_N1 and S_N2 proceeding *via* the glycosyl cation intermediate.

1.3 GLYCOSIDASE AND GLYCOSYLTRANSFERASE INHIBITORS

1.3.1 Early glycosidase inhibitors

Some of the first glycosidase inhibitors were families of monosaccharides derived from δ-aldonolactones (*e.g.* D-gluconolactone **2**) and glycosylamines (*e.g.* D-glucosamine **3**), (Figure 8).

Figure 8



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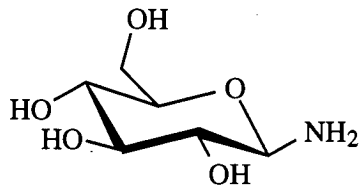

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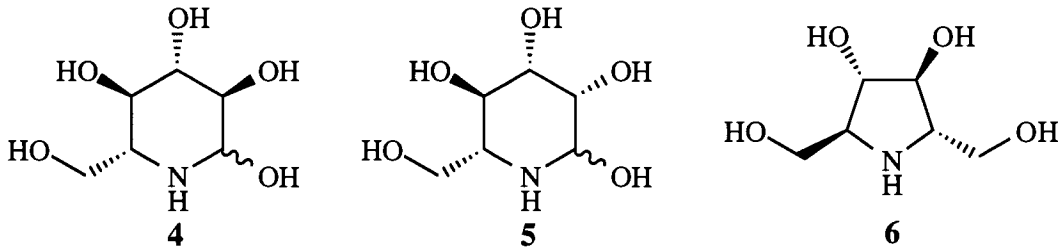
These families of compounds displayed competitive inhibition against glycosidases whose substrates they most resemble, however they lacked long term stability in aqueous solution.

1.3.2 Azasugar based inhibitors

In recent years it has been discovered that several types of polyhydroxylated piperidine and pyrrolidine alkaloids (from plants and microorganisms) are naturally occurring glycosidase inhibitors. For example nojirimycin **4** and mannojirimycin **5** are regarded as simple analogues of D-glucose and D-mannose respectively, and in the pyrrolidine series, 2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine **6** represents the analogue of

β-D-fructofuranose. These compounds are given the term 'azasugars' due to the replacement of the ring oxygen with a basic nitrogen atom, (Figure 9).

Figure 9

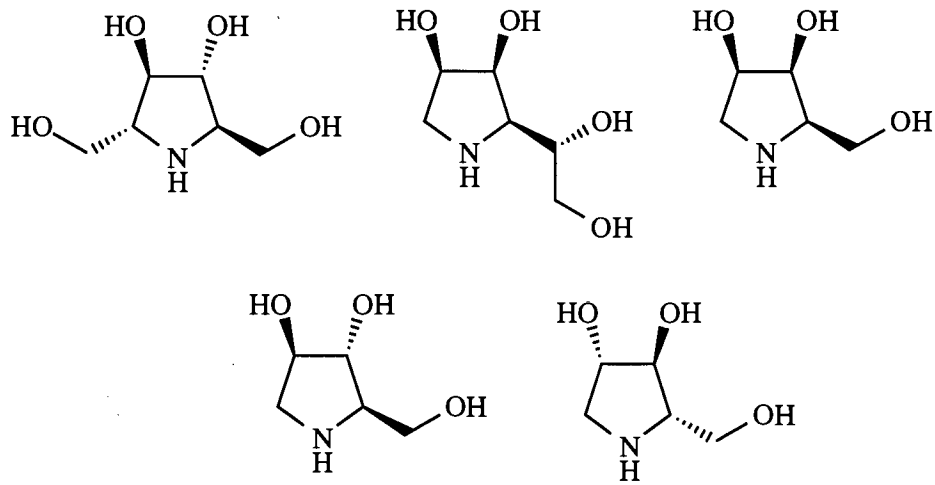


Such compounds and their 1-deoxy derivatives exert their biological activity by competitive inhibition of specific glycosidic enzymes.[23] Protonation of the azasugars at physiological pH mimics the charge distribution of the glycosyl cation developed in the transition state of the glycosidase catalysed reaction.

1.3.2.1 Five-membered azasugars as inhibitors

Polyhydroxylated pyrrolidines have a similar conformation and charge distribution to the half-chair glycosyl cation and have been found to be potent inhibitors of a wide range of glycosidases. The five azasugars shown in Figure 10 were found to be good inhibitors of various glucosidases including mannosidases and galactosidases, however none showed any inhibition of an α-L-fucosidase.[24]

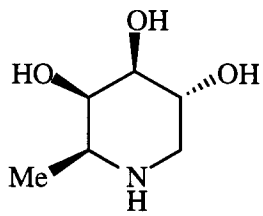
Figure 10



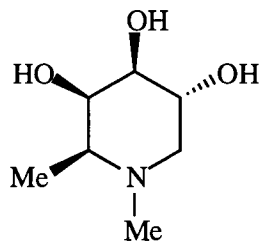
1.3.2.2 Six-membered azasugars as inhibitors.

Azasugars including (-)-deoxyfuconojirimycin (DFJ) **7** and its derivatives have been found to be potent inhibitors of α-L-fucosidases.[25-27] To investigate the effects on stereochemical and functional group changes on the core structure of DFJ, a number of derivatives **8-11** were synthesised and assayed as inhibitors of several glycosidases (Figure 11, the K_i values shown are those obtained from an assay against a human liver α-L-fucosidase). DFJ **7** was not only found to be a very potent inhibitor of the human liver α-L-fucosidase but also very specific as the other 11 glycosidases assayed were not inhibited to any extent. *N*-Methylation to give the analogue **8** had very little effect on competitive inhibition of the α-L-fucosidase, however it did broaden the specificity by showing inhibition of other glycosidases. β-Homofuconojirimycin (β-HFJ) **9** (one of the class of azasugars characterised by a hydroxymethyl group at the α-position of the sugar) retained inhibitory activity. (-)-Deoxymannojirimycin (DMJ) **10** showed poor fucosidase inhibition but was the only derivative to show mannosidase inhibition suggesting that mannosidases are sensitive to substituents at C_1. Finally, 6-epi-α-homofuconojirimycin, **11** (the C_1-C_5 epimer of **9**) showed a considerable loss in activity.

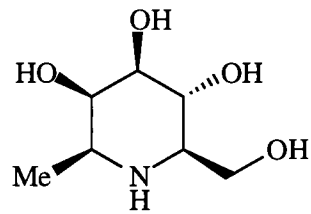
Figure 11



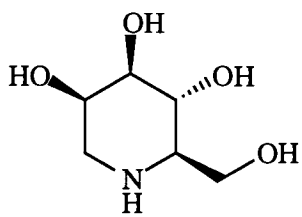
(-)-DFJ, **7**,
K_i 0.01 μM



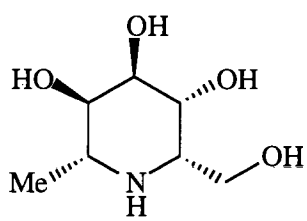
N-Me-DFJ, **8**,
K_i 0.05 μM



β-HFJ, **9**,
K_i 0.01 μM



(-)-DMJ, **10**,
K_i 5 μM

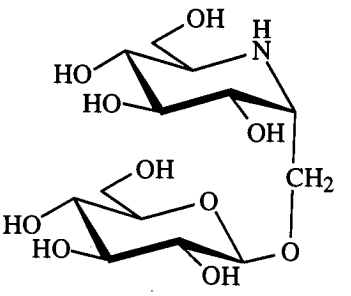


6-epi-α-HFJ, **11**,
K_i 5 μM

These azasugars exist in a 6-membered chair conformation and as a result are very specific for the enzymes whose natural substrate they inhibit. Substituents and stereochemistry of the azasugar can have a dramatic effect on the enzyme inhibition, and the results above outline the neccessity for preparation of various analogues as potential inhibitors.

A bisubstrate analogue was successfully synthesised by Liu[28] as a potent glucosidase inhibitor, (Figure 12). The transition state analogue consisted of nojirimycin to facilitate polar-polar interactions, glucose attached by a β-linkage, and also a methylene unit inserted between the two saccharide rings to mimic the lengthening of the severing glycoside linkage and to enhance its stability towards enzymatic hydrolysis. The analogue was found to be a competitive inhibitor of several glucosidases.

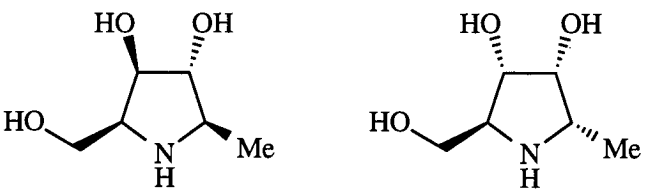
Figure 12



1.3.2.3 The synergistic inhibition of α(1,3)-FucT

Two known potent α-L-fucosidase azasugar inhibitors have been tested[12,15] against an α(1,3)-FucT and were found to be moderate inhibitors for the enzyme with IC_{50}* values 34 and 80 μM respectively (at set concentrations of acceptor, LacNAc), (Figure 13).

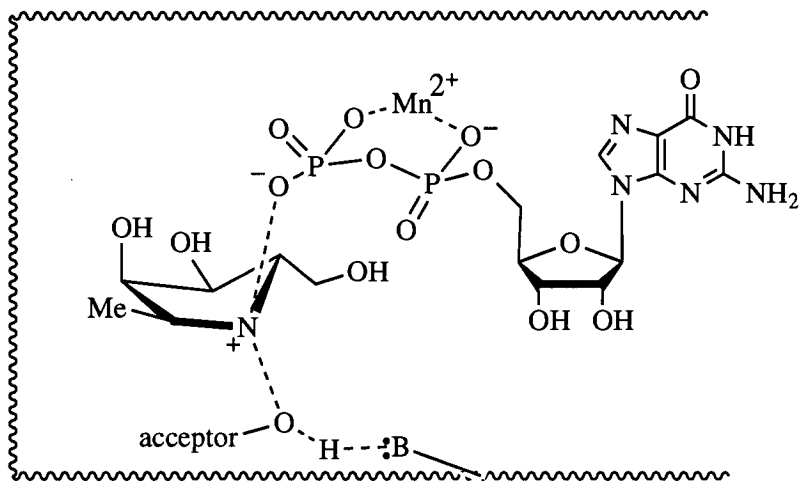
Figure 13



* *IC_{50}:- Concentration of inhibitor required to inhibit the enzyme by 50%*

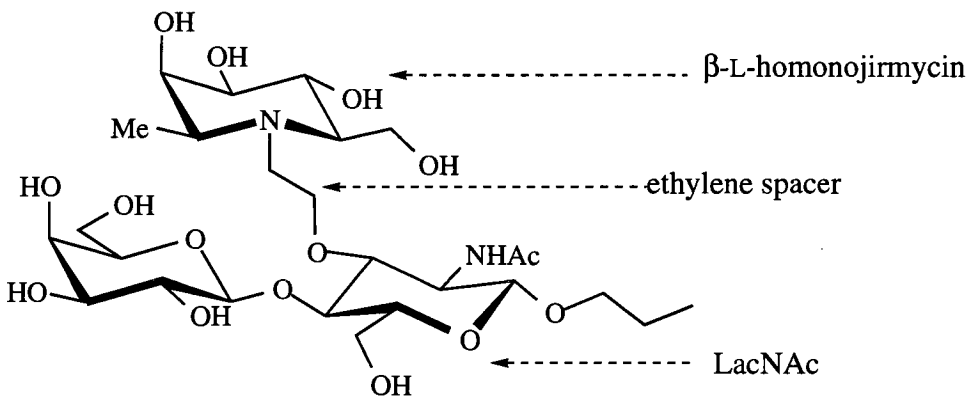
Interestingly, in the presence of GDP at the IC_{50} of the individual inhibitors, more than 80% of the enzyme was inhibited. This suggests that a possible interaction between GDP and the azasugar in the active site of the enzyme is mimicking the transition state structure of the fucosyl transfer reaction as illustrated in Figure 14. (This effect is known as synergistic inhibition).

Figure 14



On the basis of this synergism, Wong and co-workers[17] designed a potential inhibitor of an α(1,3)-FucT-V consisting of β-L-homonojirimycin covalently linked to an acceptor substrate (LacNAc). The azatrisaccharide **12** was anticipated to form a complex with GDP (of which a relatively high concentration is found in the cells) in the enzyme active site, and was found to be responsible for a 77-fold reduction (to 31 μM) of the IC_{50} in the presence of GDP.

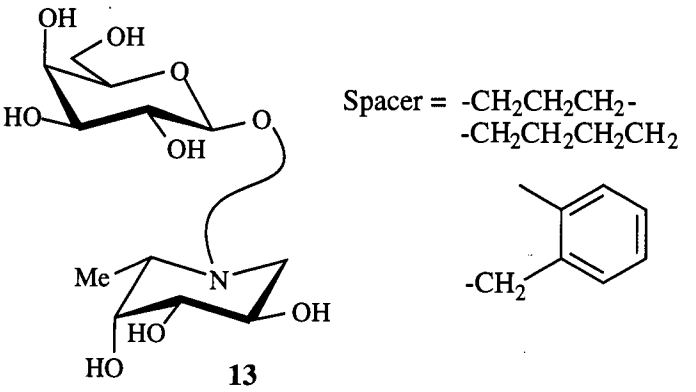
Figure 15



azatrisaccharide, **12**

A similar approach by Jefferies and Bowen[29] to a transition state mimic involved tethering the azasugar DFJ **7** to a D-galactose residue by a spacer to give the analogues **13**, (Figure 16). These azasugar analogues showed potent inhibition (IC_{50} 81-500 μM) of an α(1,3)-FucT-IV enzyme relative to DFJ (3.5 mM). A synergistic effect was also noted for the derivative containing the aromatic spacer where at a concentration of 2 μM of GDP, an IC_{50} of 50 μM was observed (IC_{50} 81 μM in absence of GDP).

Figure 16



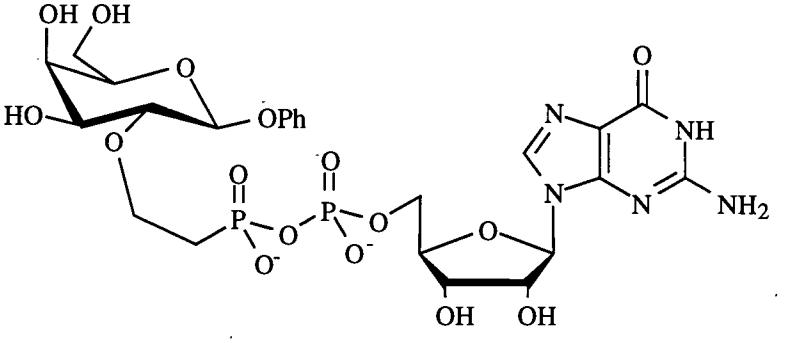
13

1.3.3 Non azasugar based inhibitors

1.3.3.1 Bisubstrate analogue as an α(1,2)-FucT inhibitor

One of the first examples of a bisubstrate analogue was designed and synthesised by Palcic *et al.*,[21] on the basis of their proposed transition state (Figure 7) of an α(1,2)-FucT. The analogue **14** contained structural elements of both donor (GDP) and acceptor sugar (phenyl-β-D-galactopyranoside) covalently attached through the acceptor hydroxyl (normally used by the enzyme). This bisubstrate analogue was found to have a K_i value of 2.3 μM with respect to the acceptor substrate, which unfortunately showed only a slight increase in inhibitory activity to GDP (K_i 8.7 μM), suggesting inhibition is strongly dependent on recognition of the GDP moiety.

Figure 17



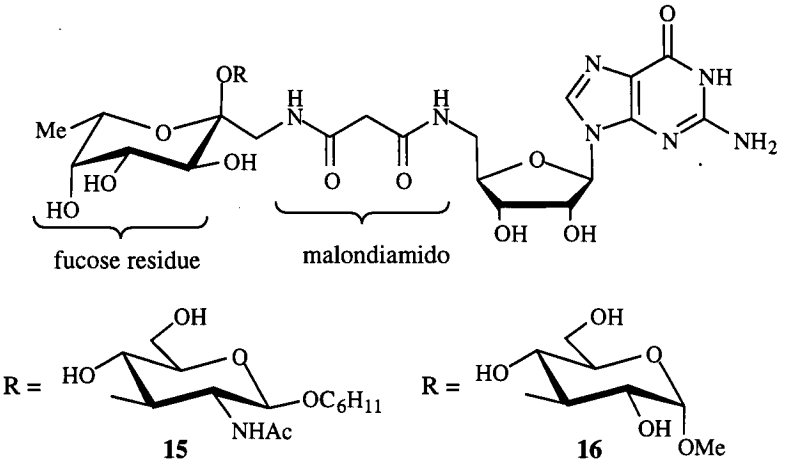
14

1.3.3.2 Trisubstrate analogues as inhibitors of α(1,3)-FucTs

Recently, van Boom and co-workers[16] embarked on the synthesis of two fucose containing trisubstrate analogues as potential inhibitors of the postulated ion-pair transition state. The proposed inhibitors **15** and **16** (Figure 18) contained a malondiamido instead of a pyrophosphate linkage between the guanosine and L-fucose moieties. It was anticipated that the non-charged amide bonds would aid membrane transport.

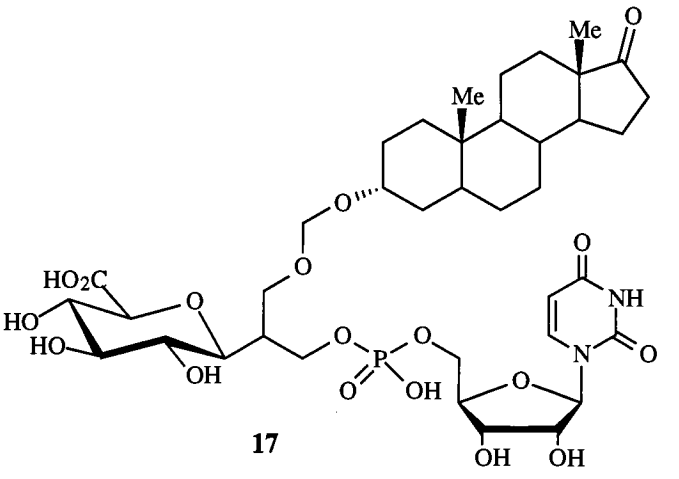
Synthesis of the potential inhibitor **15** was unsuccessful due to the acid lability of the target compound. A route to the second analogue **16** was reported, although no inhibition data was detailed.

Figure 18



Other trisubstrate analogues have been synthesised for use as inhibitors of different glycosyltransferases, for example, the trisubstrate analogue **17** (Figure 19) has shown potency as an inhibitor of several UDP-glucuronosyltransferases.[30]

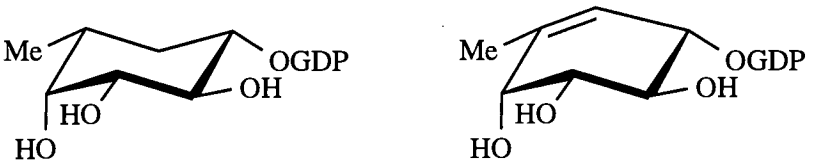
Figure 19



1.3.3.3 Carbocyclic analogues of GDP-fucose

The approach to inhibitors of fucosyltransferases by Toyokuni *et al.*,[31] involved replacement of the glycosyl moiety of the sugar nucleotide donors by a more stable carba-sugar. They reported the synthesis of two novel carbocyclic analogues **18** and **19** of GDP-fucose.

Figure 20



18 **19**

Preliminary inhibition assays carried out against α(1,3/4)-FucTs showed both **18** and **19** exhibited inhibitory activity greater than that for GDP.

1.3.3.4 Potential inhibitors using pyrophosphate mimics

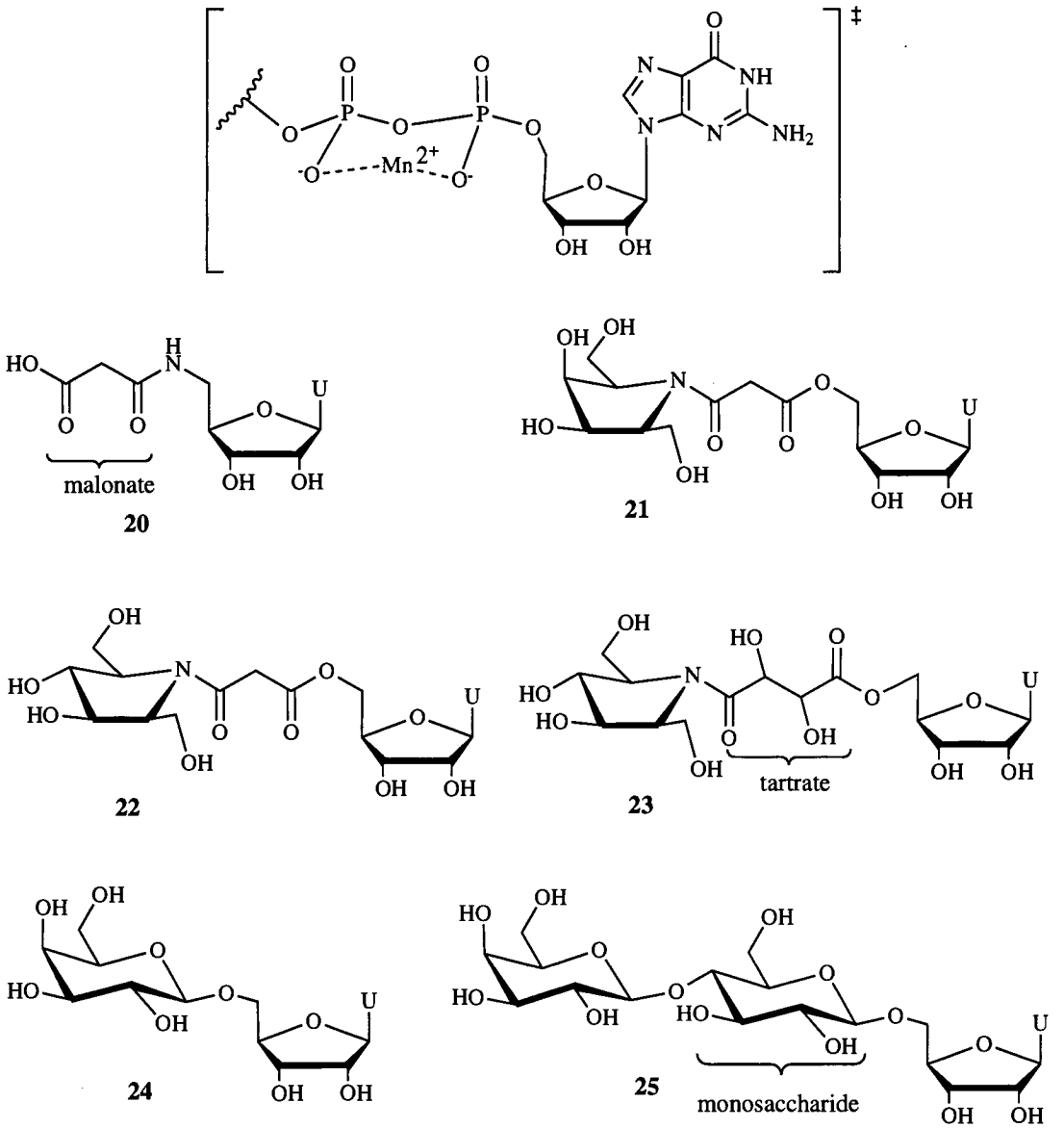
Recently, Wong and co-workers[32] have investigated the development of glycosyltransferase inhibitors using β-(1,4)-galactosyltransferase (GalT) as a model system. This enzyme catalyses the transfer of galactose from UDP-galactose to an acceptor sugar and is proposed to proceed *via* a transition state analogous to that of the FucT in Figure 7.

Attention was focused on the development of pyrophosphate analogues that would be capable of mimicking the pyrophosphate-metal ion cofactor interaction thought to form a 6-membered ring complex as depicted in Figure 21. Malonate, tartrate and monosaccharide linkages were chosen as pyrophosphate mimics on the basis of other galactosyltransferase inhibitors, and it was proposed that the malonate and tartrate esters could form a 6-membered complex with Mn^{2+}, and that the monosaccharide unit could mimic the 6-membered ring conformation. The compounds shown in Figure 21 were synthesised and their inhibitory activities assessed.

The malonate analogues **20** and **22** showed no inhibition of the GalT, however analogue **21** did show some inhibition (K_i 1 mM) but was much less effective than UDP (K_i 460 μM). Compounds **21** and **22** were expected to show better activity due

to protonation of the azasugar at physiological pH which would mimic the half-chair conformation of the glycosyl cation developed in the proposed transition state. Despite this, the results suggested that the malonic ester moiety was a very poor pyrophosphate substitute. An interesting factor in the difference in activity of **21** and **22** (the only difference in structure being the configuration at C-3 in the azasugar) is paralleled in the inhibition of galactosidase where the azasugar portion of **21** is a better inhibitor than that of compound **22**, strengthening the concept that glycosyltransferase reactions possess a similar donor transition state structure to the corresponding glycosidase reactions.

Figure 21



U = Uridine base

Compound **23** also showed no inhibition towards the GalT, and **24** was also found to be a poor inhibitor (K_i 1 mM). Interestingly, analogue **25** was a moderate inhibitor (K_i 120 μM) suggesting the pyrophosphate-metal ion complex may be mimicked by the glucose residue and that this conformation may be crucial for transferase recognition.

Other work has been reported into the synthesis of pyrophosphate mimics incorporating a (1,1-difluoromethylene)phosphate group at the C-2 position of a hydroxylated piperidine but no inhibition assays were given.[33]

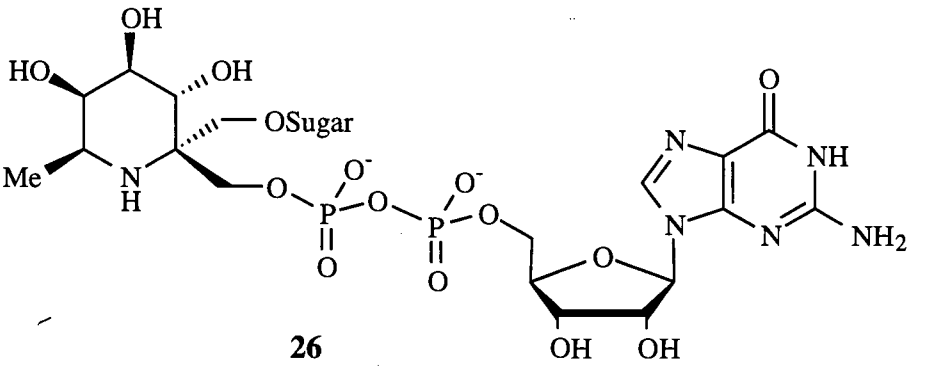
1.4 PROJECT AIM AND INHIBITOR DESIGN

The aim of the project was to design and synthesise compounds as potential inhibitors of human α(1,3)-FucTs which are involved in the biosynthesis of sialyl Lewis-X, **1**. This may enable control of the flow of leukocytes to the site of injury in the inflammatory response and result in the development of potential therapeutic agents.

The inhibitor design was based on a combination of known inhibitors of α-L-fucosidases and α(1,3)-FucTs (and related enzymes) and also on the postulated transition state of the latter.[21] As a result a novel trisubstrate analogue **26** was designed consisting of an azasugar, a GDP unit and a sugar residue.

It was anticipated that the azasugar, based on deoxyfuconojirimycin which contains all the peripheral orientation and stereochemistry of fucose, would be protonated on the nitrogen *in vivo* and hence mimic the glycosyl cation generated in the transition state of the enzymatic fucose transfer. It was also reasoned that the *O*-linked GDP and sugar unit would mimic the presence of the corresponding groups in the transition state. Insertion of the methylene units between these residues and the azasugar is expected to prevent hydrolytic cleavage of the substituents whilst mimicking the lengthening of the glycoside bond forming and nucleotide bond breaking process.

Figure 22

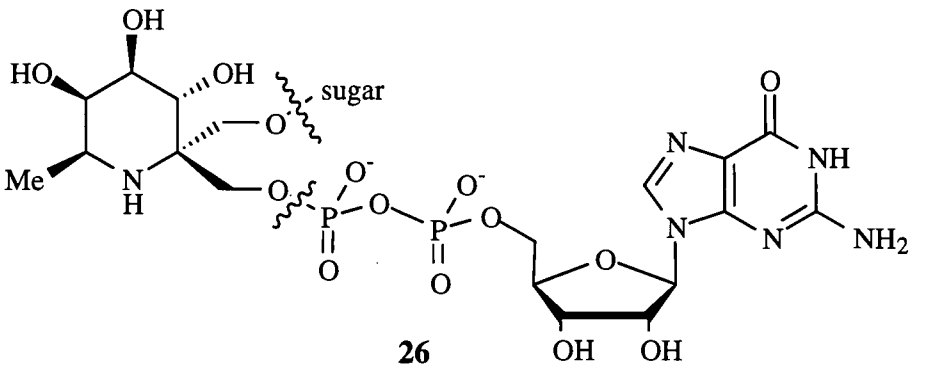


26

Sugar =Glu, GlcNAc, Gal.

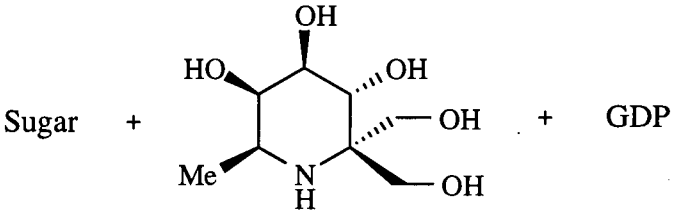
A retrosynthetic disconnection of the trisubstrate analogue **26** as indicated in Figure 23 reveals three fragments- a *bis*-hydroxymethylpiperidine **27**, a sugar and the GDP residue. The synthetic challenge of the trisubstrate **26** lies in the ability to prepare the azasugar unit **27** and the following section details some of the previous syntheses of azasugars. A more in depth retrosynthetic analysis is detailed in section 2.1.

Figure 23



26

C-O disconnection



27

1.5 PREVIOUS AZASUGAR SYNTHESES

1.5.1 Carbohydrates as starting materials

Due to the presence of 3 or 4 contiguous chiral centres, the majority of syntheses of homochiral azasugars have begun with carbohydrates from the chiral pool. This approach enables the retention of some of the existing sugar stereochemistry and functionality in the azasugar product.

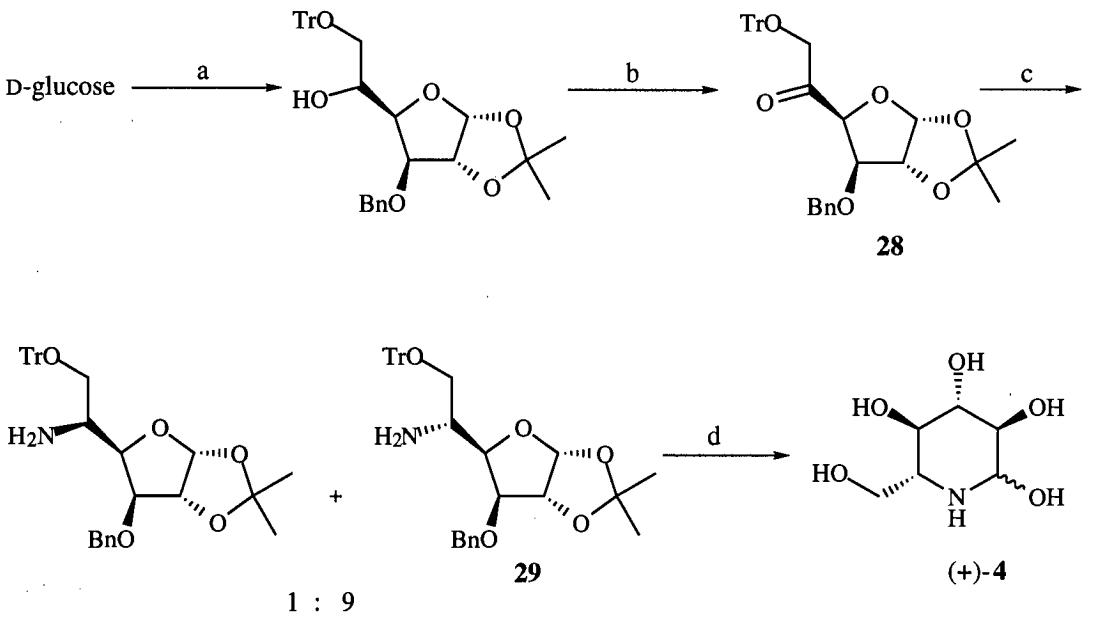
Utilising carbohydrates requires the introduction of nitrogen and the formation of the piperidine ring between C-1 and C-5, or pyrrolidine between C-1 and C-4. Common methods of achieving this rely on:- 1) introduction of the nitrogen by S_N2 displacement of a good leaving group by azide followed by hydrogenation; or 2) by oxidation of an appropriate 2° hydroxyl group, followed by oxime formation and stereoselective reduction (reductive amination).

Outlined below, are some selected syntheses of several key azasugars from carbohydrates.

i. (+)-Nojirimycin

The first synthesis of (+)-nojirimycin **4** was achieved by Inouye *et al.*, from D-glucose,[34] and involved oxidation of the secondary hydroxyl to give the ketone **28**. Oxime formation followed by reduction and deprotection yielded the amine **29** which was subjected to a final deprotection to give the target azasugar, (Scheme 1).

Scheme 1

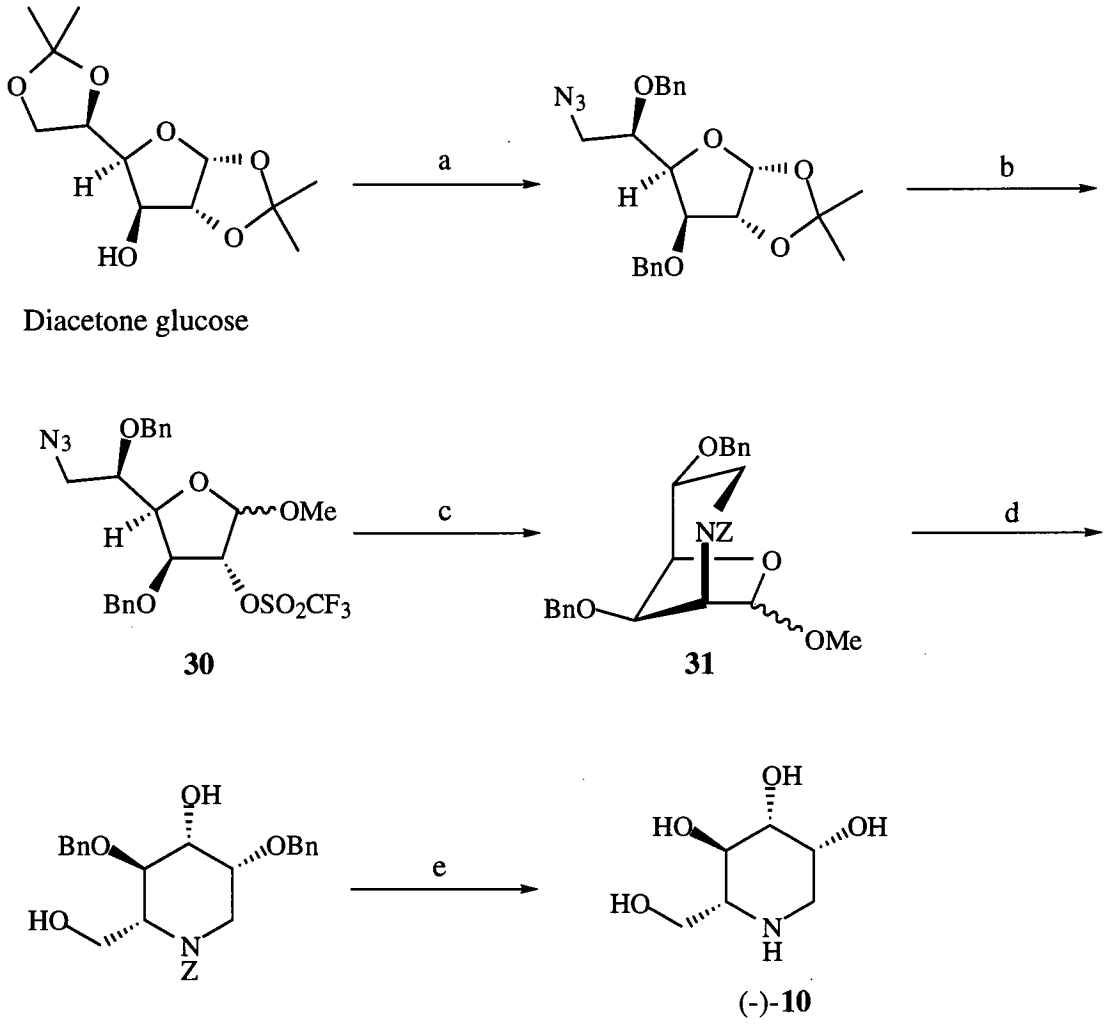


Reagents and conditions: (a) 4 steps, 46%, (b) DMSO, Ac_2O, 73%. (c) i. $NH_2OH.HCl$, MeOH, crude. ii. Raney Ni, MeOH, $NH_3(l)$, 94%. (d) i. $Li/NH_3(l)$, -70°C, 74%. ii. SO_2, H_2O, 40°C, 96%. iii. Dowex IX2 (OH) resin, quantitative.

ii. (-)-Deoxymannojirimycin

A ten step synthesis from diacetone glucose has been developed for the synthesis of (-)-deoxymannojirimycin **10**, in an overall yield of 35% and on a moderate scale.[35] Piperidine ring formation was achieved by an intramolecular nucleophilic displacement of a triflate at C-2 in compound **30** by an amine at C-6 (generated *in situ*) to give the cyclised amine **31**, (Scheme 2).

Scheme 2

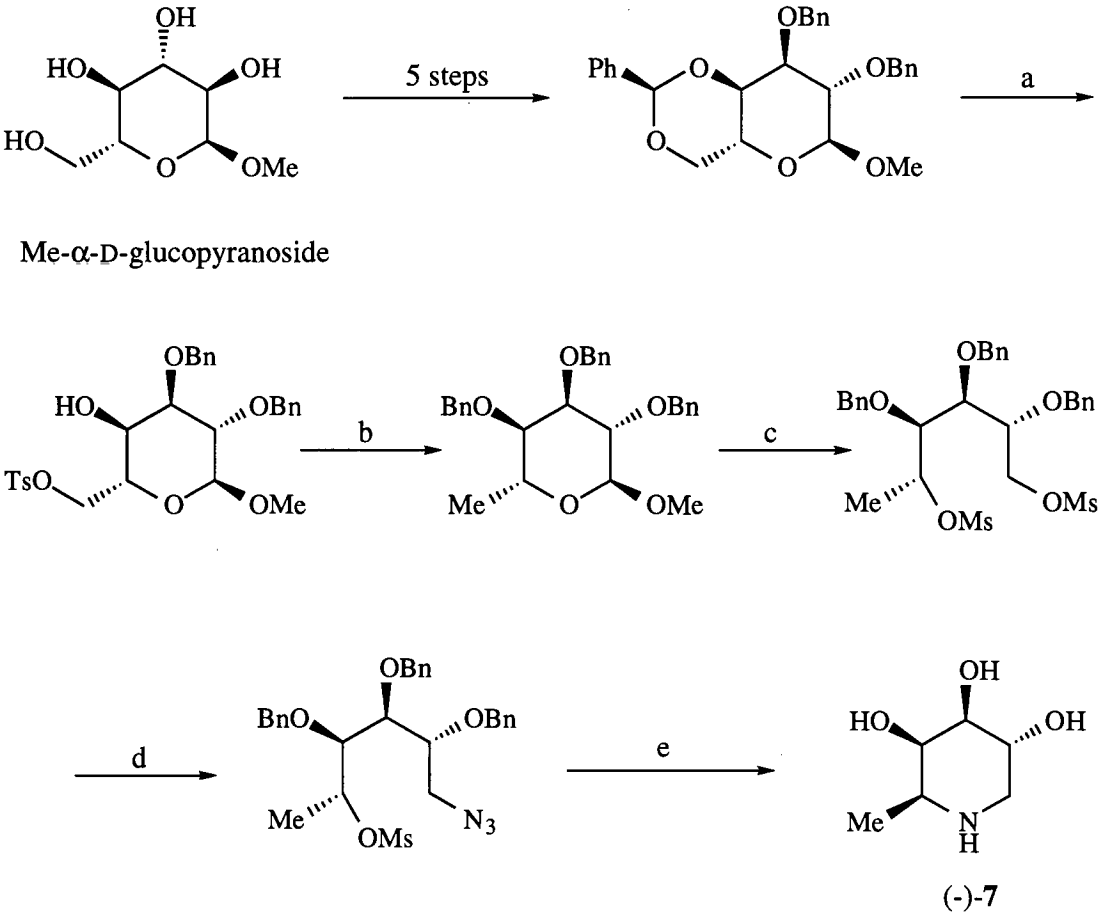


Reagents and conditions: (a) i. aq. acetic acid. ii. TsCl, pyridine, -14°C, 92% (2 steps). iii. NaN_3, DMF, 40°C, 92%. iv. NaH, BnBr, Bu_4NI, THF, 68%. (b) i. acidic methanol, 96%. ii. triflic anhydride, DCM, pyridine, 97%. (c) i. Ph_3P, DCM, then K_2CO_3. ii. $PhCH_2CO_2Cl$, ether, 82% (2 steps). (d) i. aq. TFA, 85%. ii. $NaBH_4$, aq. EtOH, 94%. (e) H_2, Pd-C, acetic acid 95%.

(iii) (-)-Deoxyfuconojirimycin

The first synthesis of DFJ **7**, required connection of C-1 and C-5 of methyl α-D-glucopyranoside with nitrogen, inversion of configuration at C-2 and C-3 and deoxygenation of C-6.[26] Introduction of the nitrogen proceeded *via* an S_N2 displacement of a mesylate by azide followed by a reductive amination, (Scheme 3).

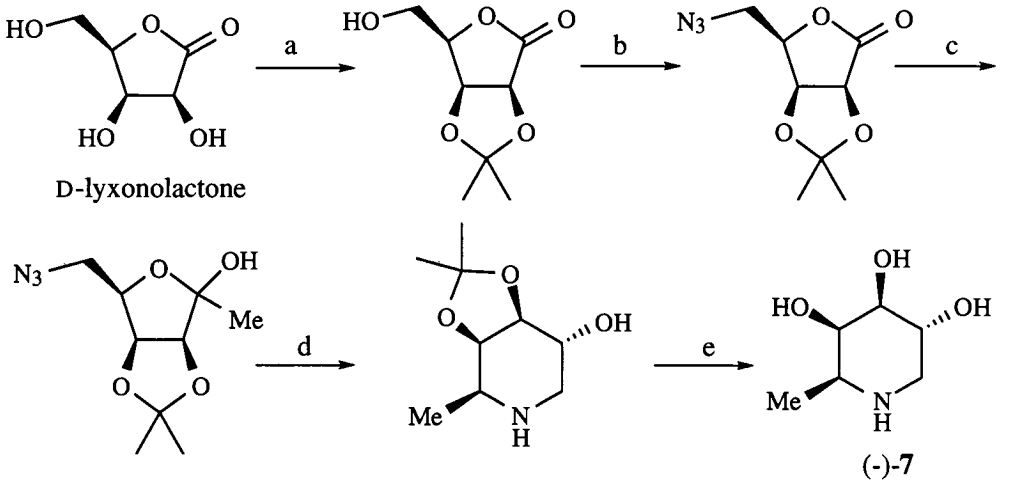
Scheme 3



Reagents and conditions: (a) i. acetic acid:water (4:1). ii. TsCl, pyridine, -20°C, 75% (2 steps). (b) i. $LiAlH_4$, THF. ii. BnBr, NaH, Bu_4NI, THF, 64% (2 steps). (c) i. TFA:H_2O (4:1). ii. $NaBH_4$, EtOH, 85% (2 steps). iii. 3 eq. MsCl, pyridine, 0°C. (d) Bu_4NN_3, DMF, 60% (2 steps). (e) i. sodium hydrogen telluride, 75%, ii. H_2, Pd-C, EtOH, quantitative.

Several years later, a more practical and efficient synthesis was reported.[36] This synthesis utilised only one isopropylidene protecting group, was completed in 5 steps from D-lyxonolactone in a yield of 41% and could be performed on a multigram scale, (Scheme 4).

Scheme 4



Reagents and conditions: (a) anhydrous $CuSO_4$, acetone, 60%. (b) i. Tf_2O, DCM. ii, NaN_3, DMF, 0°C, 89% (2 steps). (c) MeLi, THF, -78°C, 97%. (d) H_2, Pd-C, EtOH, 83%. (e) aq. TFA, quantitative.

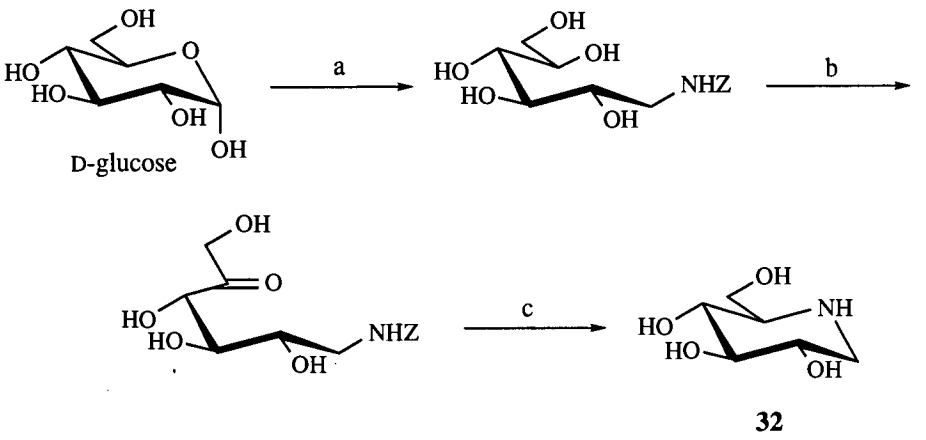
1.5.2 Chemoenzymatic syntheses

As illustrated above, many of the chemical syntheses of azasugars have required multiple protection and deprotection steps resulting in multi-step routes and low yields of products. Several chemoenzymatic syntheses have been employed as practical routes to azasugars due to their high regio- and stereoselectivity with less emphasis on a protecting group strategy. Outlined below are some of the literature reports of azasugar synthesis utilising enzymes.

1.5.2.1 Chemical-microbial synthetic approach

An enzyme mediated step has been utilised in the synthesis of (+)-deoxynojirimycin (DNJ) **32**, resulting in a 4-step synthesis of the azasugar from D-glucose.[37] Conversion of glucose to the benzyloxycarbonyl protected amine was performed and the product subjected to treatment with *Gluconobacter oxydans* which selectively oxidised the secondary hydroxyl function adjacent to the primary hydroxy group in the presence of the other hydroxyls. Subsequent intramolecular reductive amination gave (+)-DNJ in a total yield of >60% on kilogram scale, (Scheme 5).

Scheme 5



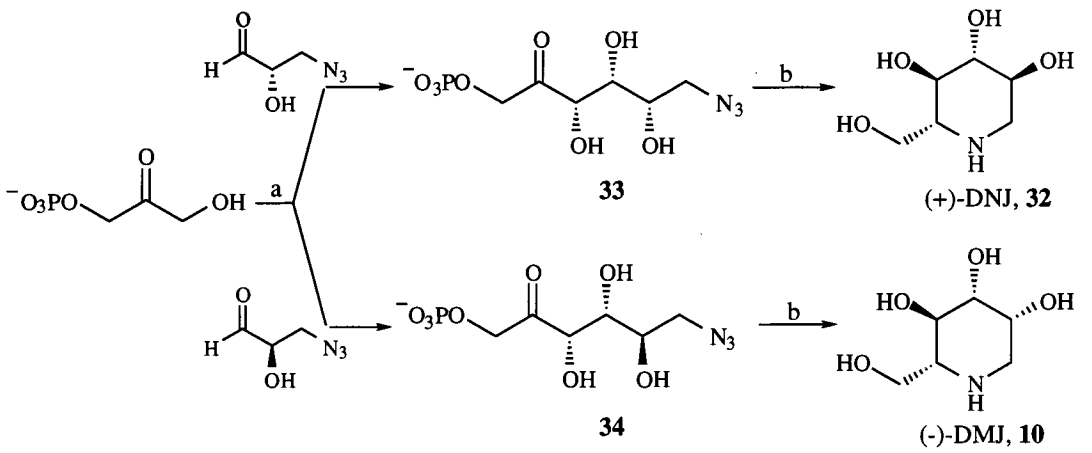
32

Reagents and conditions: (a) i. Raney Ni, NH_3(l), MeOH, H_2. ii. $PhCH_2OCOCl$, H_2O, pH 8-10. (b) *Gluconobacter oxydans*, O_2, quantitative. (c) H_2, Pd-C, MeOH/H_2O, 75%.

1.5.2.2 Use of aldolases

Aldolases are enzymes capable of catalyzing an aldol condensation and have been used in the preparation of azasugars to introduce more than one stereogenic centre.[38,39] The example given in Scheme 6 employs fructose 1,6-diphosphate aldolase (FDP-aldolase) to generate 2 chiral centres in one step with control of relative and absolute configuration.[40] The triols **33** and **34** are then dephosphorylated using a phosphatase enzyme and stereoselectively hydrogenated to give (+)-DNJ **32** and (-)-DMJ **10** *via* an imine intermediate.

Scheme 6

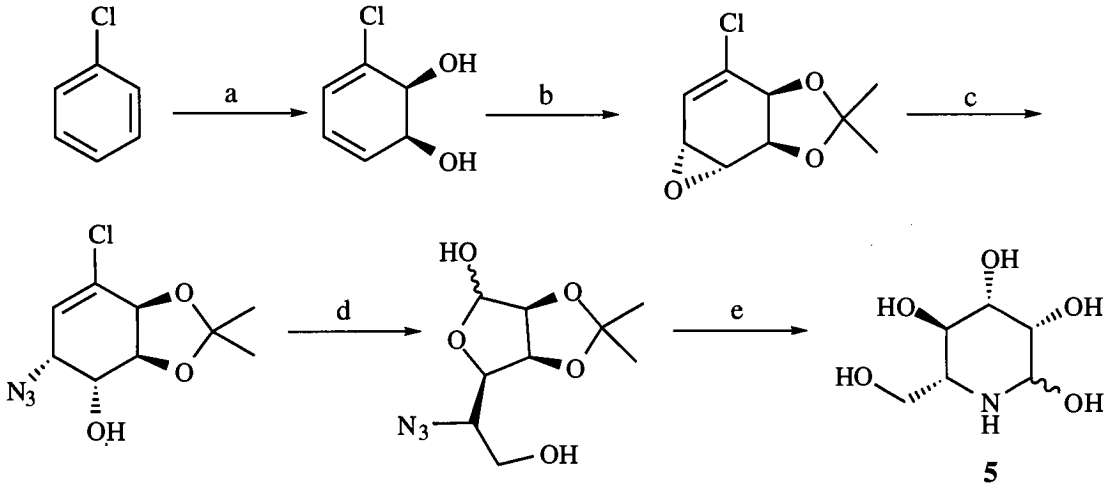


Reagents and conditions: (a) *Escherichia coli* Zn^{2+} FDP-aldolase. (b) i. acid phosphatase. ii. H_2, Pd-C.

1.5.2.3 Manipulation of cyclohexadiene-*cis*-diols

Another short synthesis of mannojirimycin **5**, was achieved *via* enzymatic hydroxylation of chlorobenzene followed by a stereoselective amination and oxidative cleavage,[41,42] (Scheme 7).

Scheme 7



Reagents and conditions: (a) *Pseudomonas putida* (39D). (b) i, 2,2-DMP, *p*TSA, DCM. ii. *m*CPBA, DCM. (c) i. LiCl, $MeCOCH_2CO_2Et$, ii. NaN_3, DMF. (d) O_3, -78°C, MeOH; $NaBH_4$. (e) i. PMe_3, $THF-H_2O$. ii. 90% aq. TFA.

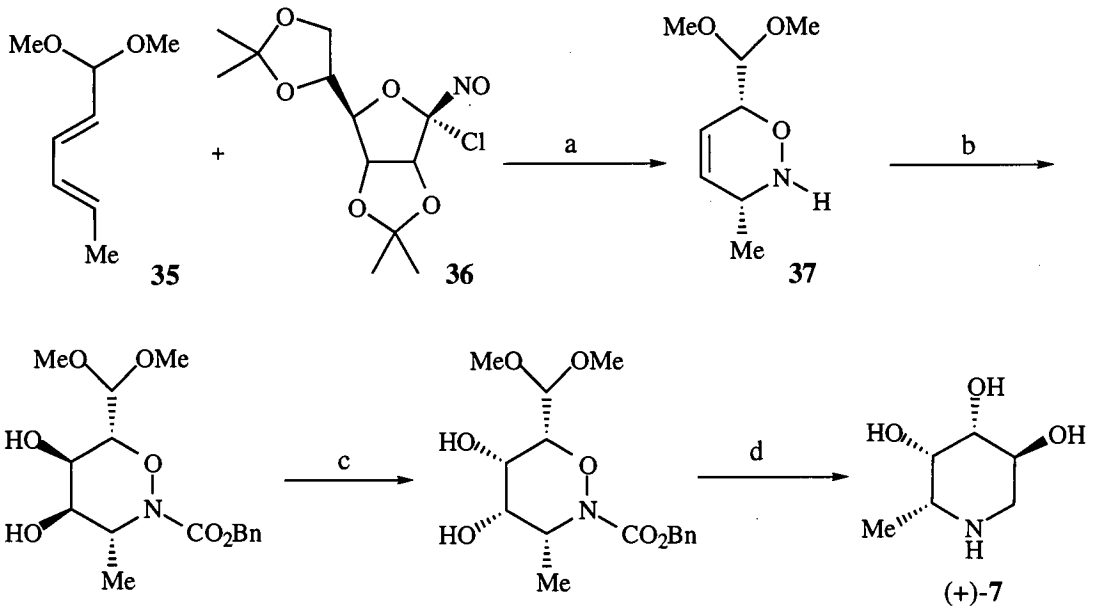
1.5.3 Alternative asymmetric syntheses

Recently, a considerable amount of attention has been focused on the asymmetric synthesis of homochiral azasugars by utilising different precursors and asymmetric techniques. Outlined below are just a few of the approaches that have been developed.

1.5.3.1 Utilising hetero-Diels-Alder cycloadditions

The hetero-Diels-Alder reaction has been employed as the key step in the synthesis of azasugars,[43] for example (+)-fuconojirimycin, (+)-allonojirimycin and their 1-deoxy derivatives.[44] Scheme 8 illustrates the synthetic route to (+)-DFJ. Reaction of the diene acetal **35** with the chloronitroso dienophile **36** gave the cycloadduct **37** after *N*-protection. A series of transformations were then required to produce the azasugar (+)-DFJ, **7**.

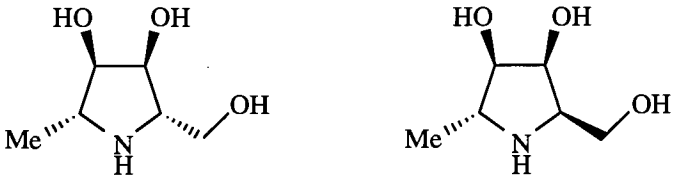
Scheme 8



Reagents and conditions: (a) i. MeOH, $HC(OMe)_3$. (b) i. $PhCH_2CO_2Cl$, ii. OsO_4, NMO, acetone:H_2O, 35% (2 steps) (c), i. Tf_2O, pyridine, 95%. ii. Bu_4NOBz, toluene. iii. Na_2CO_3, MeOH, 58% (2 steps). (d) i. H_2, Pd-C. ii. SO_2, H_2O, 42% (2 steps). iii. $Ba(OH)_2$, H_2O. iv. H_2, Pd-C, H_2O, quantitative.

A similar approach to potent glycosidase inhibitors 5-methyltrihydroxypyrrolidines has also been applied.[45]

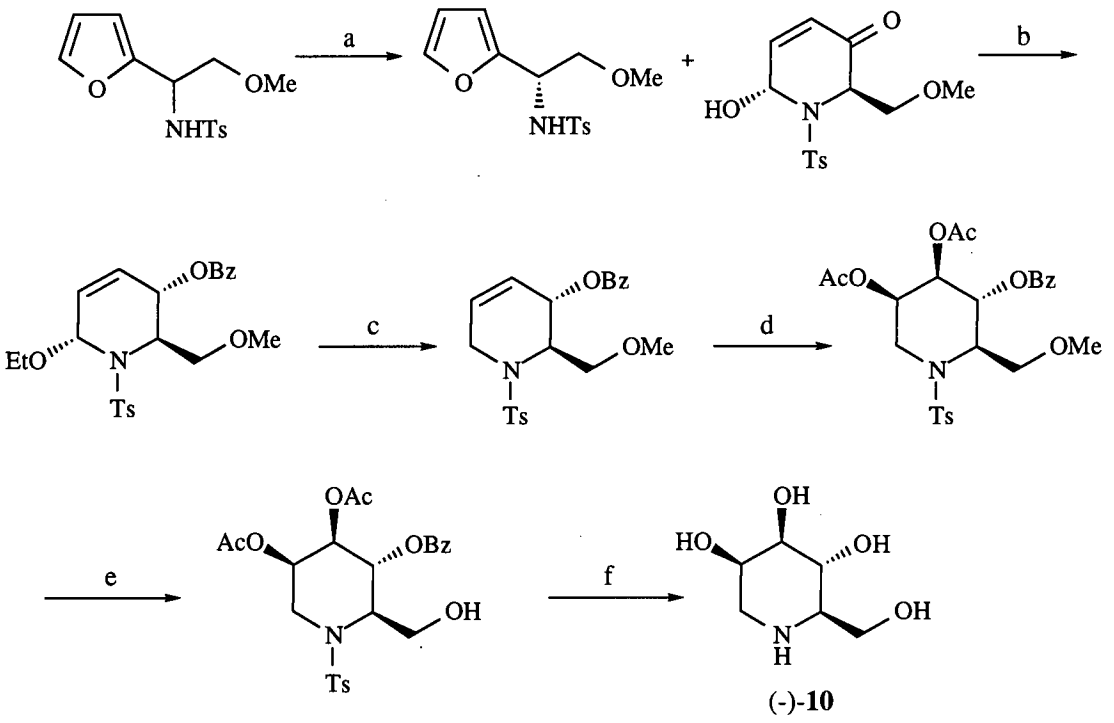
Figure 24



1.5.3.2 Use of kinetic resolution to afford a flexible building block

An efficient method for the kinetic resolution of α-furfuryl amide using a modified Sharpless asymmetric epoxidation reagent has been used to afford chiral building blocks suitable for the synthesis of many types of alkaloids[46-48] and is illustrated for (-)-DMJ, **10**, (Scheme 9).

Scheme 9



Reagents and conditions: (a) i. $Ti(O^iPr)_4$, L-(+)-DIPT, TBHP, silica gel, CaH_2, DCM. (b) i. $HC(OEt)_3$, $BF_3.OEt_2$, THF, 0°C. 76%. ii. $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -30°C, 72%. iii. DEAD-TPP, $PhCO_2H$, THF, 92%. (c) $NaBH_4$, HCO_2H, 0°C, 87%. (d) i. $(DHQ)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, ^tBuOH-H_2O, 85%. ii. Ac_2O, DMAP, pyridine, 100%. (e) BBr_3, DCM, -78°C, 72%. (f) Na-naphthalene, DME, -60°C, 51%.

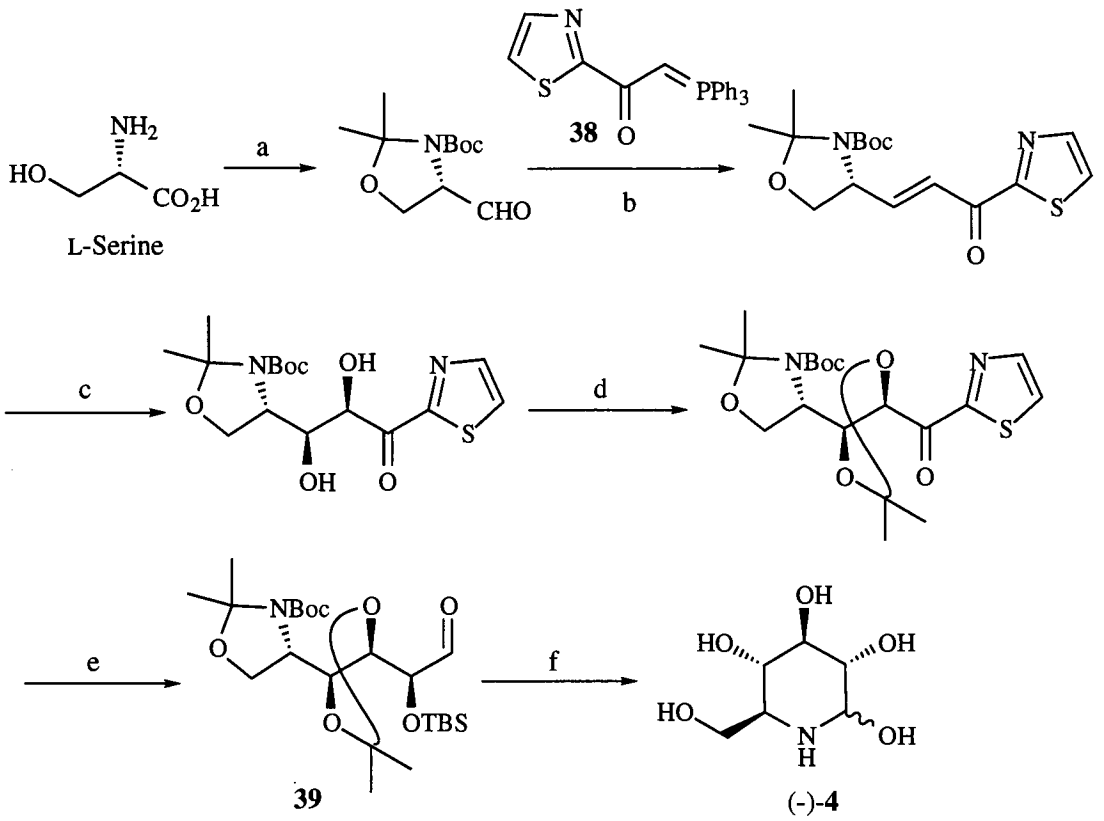
1.5.3.3 From amino acids

There are surprisingly few syntheses of azasugars which employ natural amino acids as starting materials. Examples of the main strategies are outlined below.

i. From serine

Dondoni *et al.*,[49-51] have synthesised several azasugars from L-serine, including (-)-nojirimycin *via* a thiazole intermediate acting as a protected aldehyde, (Scheme 10). Addition of the stabilised carbonylphosphorane **38** to the aldehyde derived from L-serine, gave the *E*-enone which underwent *cis*-dihydroxylation to gave a mixture of diols (86:14, *anti*:*syn*) separable by column chromatography. Stereochemically controlled reduction of the carbonyl gave the required diastereomer (ds >95%) followed by a one pot thiazoyl-to-formyl unmasking procedure to reveal the aldehyde **39**, which was then carried through to (-)-deoxynojirimycin, (-)-**4**.

Scheme 10

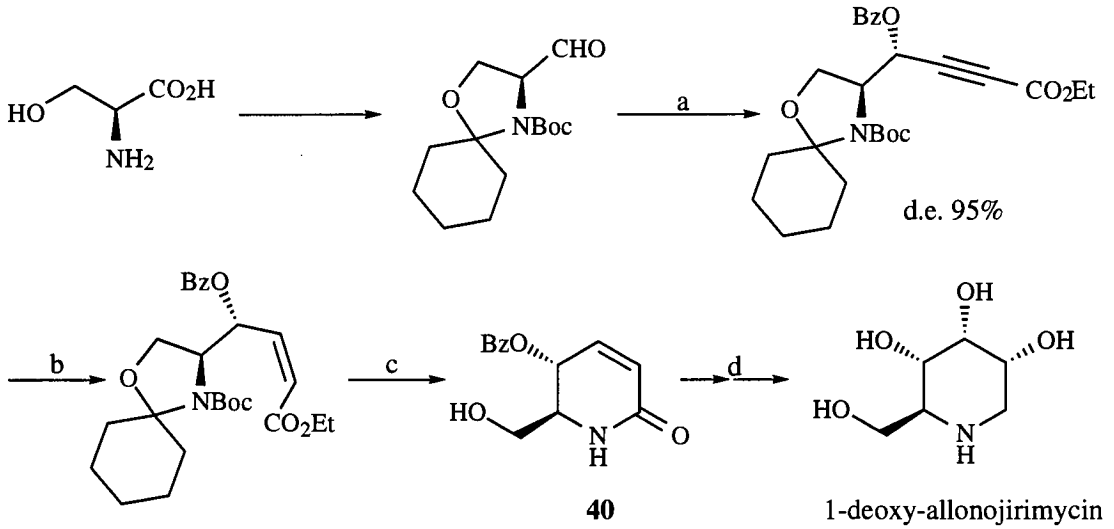


Reagents and conditions: (a) i. Boc_2O, 1,4-dioxane, 0°C, pH 10. ii. CH_2N_2, ether, 0°C, 80-90% (2 steps). iii. 2,2-DMP, *p*TSA, benzene, reflux. iv. DIBAL, toluene, -78°C, 76%. (b) i. **38**, toluene, reflux, 90%. (c) OsO_4, NMO, ^tBuOH, H_2O, 60%. (d) 2,2-DMP, *p*TSA, benzene, reflux, 94%. (e) i. $NaBH_4$, MeOH, 60°C, 96%. ii. TBSCl, imidazole, DMF, -80°C, 85%. iii. MeI, MeCN, reflux, 82%. iv. $NaBH_4$, MeOH. v. $HgCl_2$, MeCN, H_2O, 82% (2 steps). (f) aq. TFA, 80%.

Altenbach and Himmeldirk[52] also utilised L-serine to synthesise a dihydropyridine derivative **40** as a key intermediate for use as a building block for the synthesis of azasugars, the strategy is outlined in Scheme 11.

Finally, Dalton *et al.*,[53] also applied L- and D-serine as precursors for the synthesis of a number of polyhydroxylated pyrrolidines.

Scheme 11

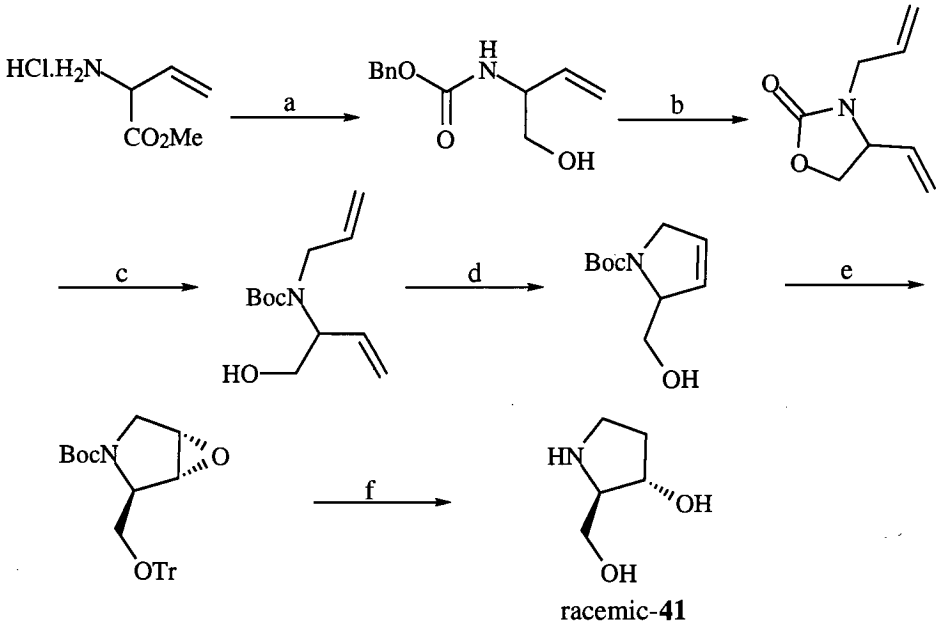


Reagents and conditions: (a) i. $HCCCO_2Et$, *n*BuLi, THF, HMDT, -90→-35°C. ii. BzCl, -50°C. (b) Lindlar catalyst, EtOAc, quinoline. (c) i. Ether/H_2O/TFA (1:1:3). ii. EtOAc, sat. aq. $NaHCO_3$. (d) 6 steps.

ii. From vinyl glycine methyl ester

A strategy for the synthesis of 2-hydroxymethyl-3-hydroxypyrrolidines was developed using a ruthenium catalysed olefin methathesis as key step for ring formation.[54] Scheme 12 illustrates the route used for the preparation of *rac-trans*-2-hydroxymethyl-3-hydroxypyrrolidine, **41**.

Scheme 12

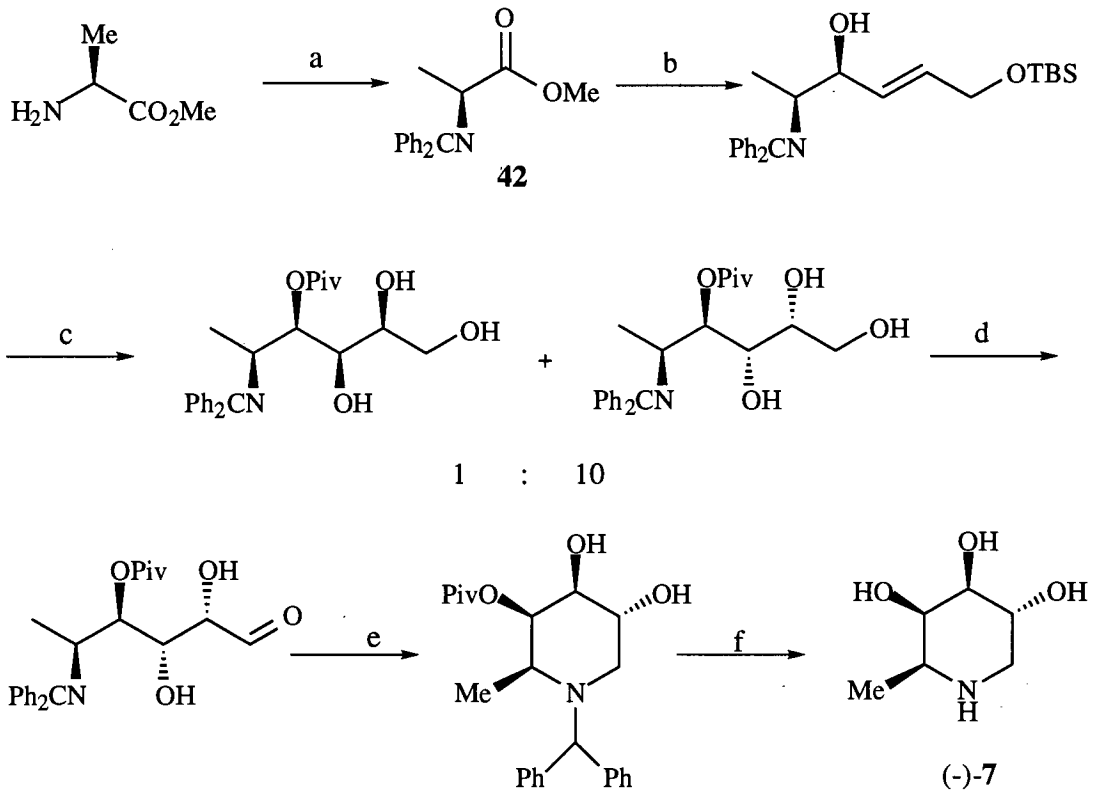


Reagents and conditions: (a) i. $PhCH_2OCOCl$, $NaHCO_3$, H_2O, DCM, 45%. ii. $LiBH_4$, MeOH, ether, 81%. (b) NaH, DME, then $BrCH_2CH{=}CH_2$, 92%. (c) i. NaOH, H_2O, EtOH, reflux. ii. Boc_2O, Et_3N, DCM, 82%. (d) $Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2$ (4 mol%), benzene, 95%. (e) i. Ph_3CCl, DMAP, Et_3N, DCM, 93%. ii. *m*CPBA, ether, 75%. (f) i. $LiBH_4$, MeOH, diglyme, 150°C, 85%. ii. HCl, MeOH, 90%.

iii. From L-alanine

Polt and Sames[55] synthesised (-)-deoxyfuconojirimycin **7**, utilising a Schiff base protection of the chiral α-amino ester derived from L-alanine. Stereoselective C-C bond formation with chelation control followed by further functionalisation gave (-)-DFJ in 20% yield in 8 steps from the alanine Schiff base **42**, (Scheme 13).

Scheme 13

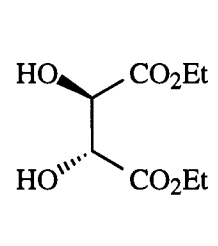


Reagents and conditions: (a) $Ph_2C{=}NH$, DCM, 93%. (b) i. $^iBu_5Al_2H$, ii. Li-CH=CH-CH_2OTBS, 70%, (2 steps). (c) i. Pivolyl protection, (no details given). ii. $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $^tBuOH/H_2O$, 70%. iii. TBAF, THF, 99%. (d) TEMPO, NaOCl, DCM/H_2O. (e) $NaBH_3CN$, HOAc, H_2O, pH 5, 75-80% (2 steps). (f) i. $n Bu_4NOH$, 1,4-dioxane, H_2O, 80%. ii. H_2, Pd-C, MeOH, 95%..

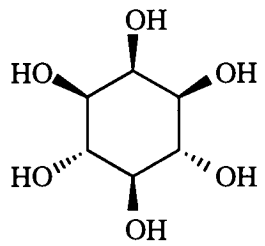
1.5.3.4 Additional non-carbohydrate based precursors

Asymmetric synthesis of azasugars have been successfully developed utilising precursors other than those mentioned above, for example diethyl tartrate[56-58], *myo*-inositol,[59,60] and very recently from achiral building blocks such as dihydropyran.[61] Other groups have proceeded *via* ring opening operations on bis-aziridines[62] and also on C_2-symmetric bis-epoxides[63] by amines, all of which are shown in Figure 25.

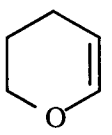
Figure 25



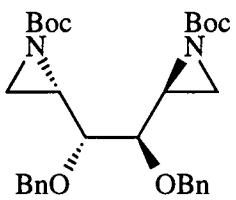
Diethyl tartrate



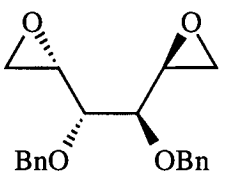
myo-inositol



Dihydropyran



Bis-aziridine



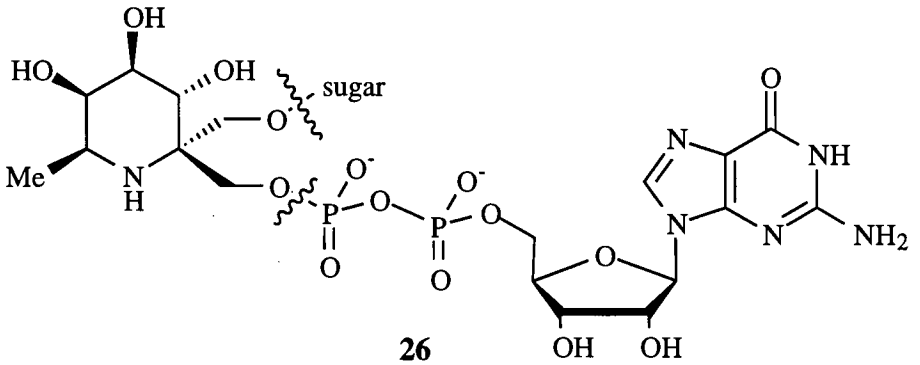
Bis-epoxide

2. RETROSYNTHESIS

2.1 RETROSYNTHETIC ANALYSIS OF THE TRISUBSTRATE ANALOGUE 26

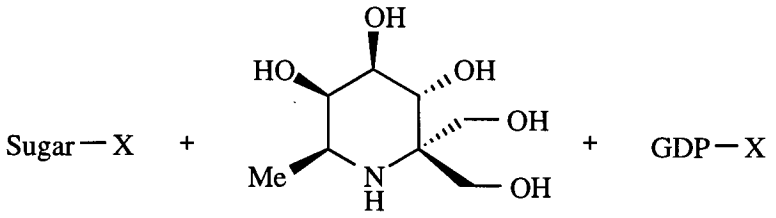
An initial disconnection in the retrosynthetic analysis of the target molecule **26** is illustrated in Scheme 14. Disconnection of the C-O and P-O bonds connecting the sugar and GDP moieties reveals an azasugar with a *bis*-hydroxymethyl unit, a sugar and a GDP residue.

Scheme 14



26

C-O disconnection



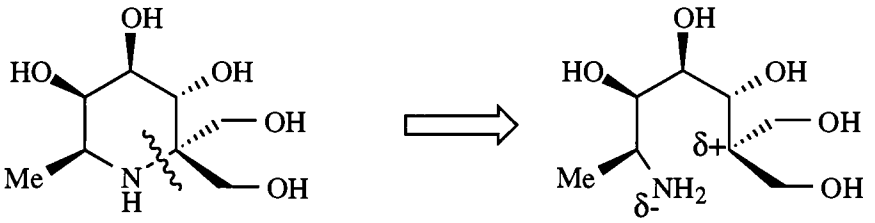
27

It was envisaged that formation of the glycoside-azasugar bond could be achieved by S_N2 displacement by the primary hydroxyl function of **27** of an appropriate leaving group on the glycoside donor, sugar-X.[64]

Assembly of the GDP moiety is well established and can be achieved by initial phosphitylation of the primary hydroxyl function at C-2 (using a suitable hydroxyl protected derivative of **27**) with dibenzyl, *N*,*N*-diisopropyl phosphoramidite and 1*H* tetrazole, followed by oxidation with *meta*-chloroperbenzoic acid.[65] Birch reduction to remove the benzyl groups would then allow coupling to GMP-morpholidate under standard conditions.[66,67]

A further disconnection of the *bis*-hydroxymethyl piperidine **27** at the N-C2 bond reveals an acyclic system **43** containing 5 contiguous stereocentres, whereby ring formation may result from attack of a nucleophilic amine onto an electrophilic carbon, (Scheme 15).

Scheme 15

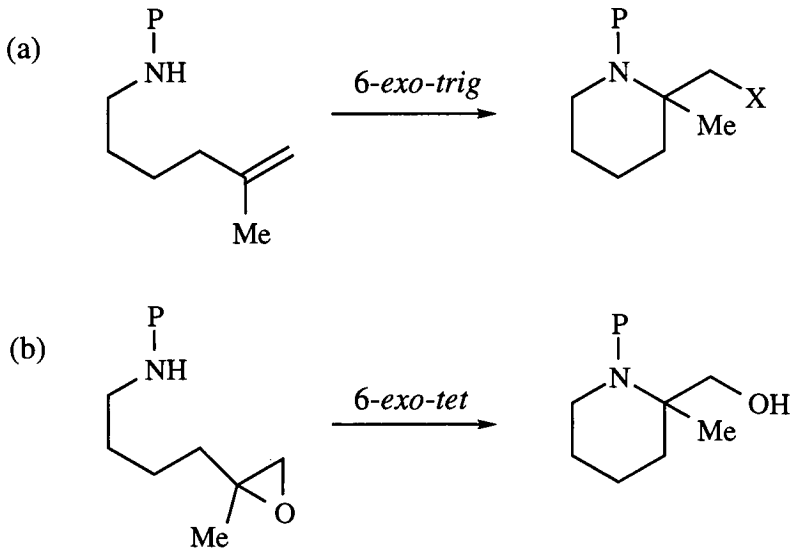


27 **43**

Previous work within the group involved a study of the ring closing ability of an acyclic unfunctionalised amine onto an electrophilic carbon species as a potential route to piperidine formation.[68] Initially, a 6-*exo-trig* cyclisation was investigated utilising different nitrogen protecting groups, (Scheme 16a). Mercury (II) metal cation mediated cyclisation was attempted using mercuric acetate and mercuric trifluoroacetate but none of the desired piperidine was observed (X = HgOAc or $HgOCOCF_3$). Intramolecular cyclisation of the *N*-Tosyl protected amino alkene was effected smoothly by treatment with the organoselenium reagent *N*-phenylselenophthalimide (*N*-PSP) to give the cyclised product (X = SePh) in excellent yield (92%). Unfortunately, oxidation of the C-Se bond to a C-O bond proved problematic and only proceeded in 27% over 2 steps.

An intramolecular 6-*exo-tet* cyclisation of an amine onto a *gem*-disubstituted epoxide was also investigated, (Scheme 16b). Cyclisation was effected only in the presence of the Lewis acid, boron trifluoride etherate ($BF_3.OEt_2$) and only with the *N*-Tosyl protected amine in a yield of 56%. Use of other Lewis acids ($TiCl_4$) and bases (NaH, NaOH) failed to give any of the desired product.

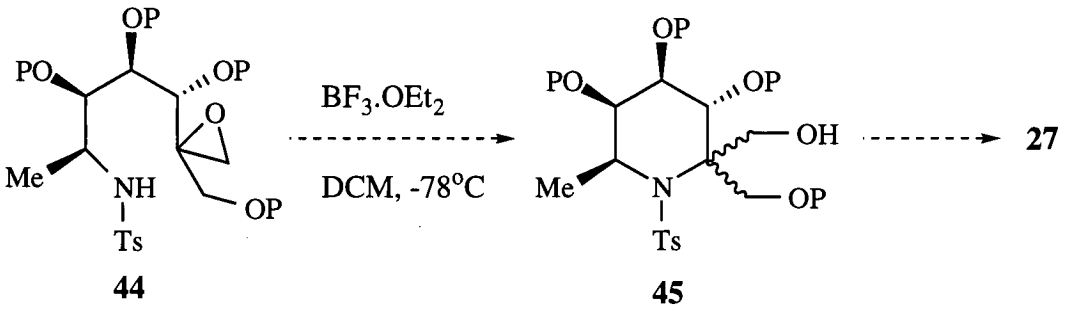
Scheme 16



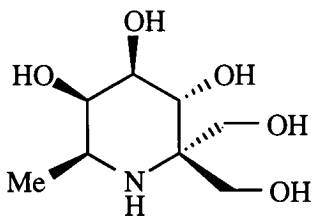
P = CO_2Et, CO_2Bu^t, CO_2Bn, COMe, $COCF_3$, SO_2Bn, Ts.

From these model studies it was proposed that a route to the functionalised piperidine **27** could be developed by an intramolecular 6-*exo-tet* cyclisation of an *N*-Tosyl protected amine onto a disubstituted epoxide **44**, (Scheme 17).

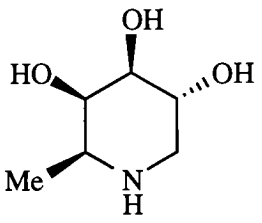
Scheme 17



Due to the complexity of the functionalised azasugar **27**, a simplified azasugar (-)-deoxyfuconojirimycin **7** was the target for initial synthesis. (-)-DFJ contains four of the required stereocentres of **27** and it was envisaged that development of a synthetic route to **7** would enable elaboration of the synthesis to form the required azasugar **27**.



27



7

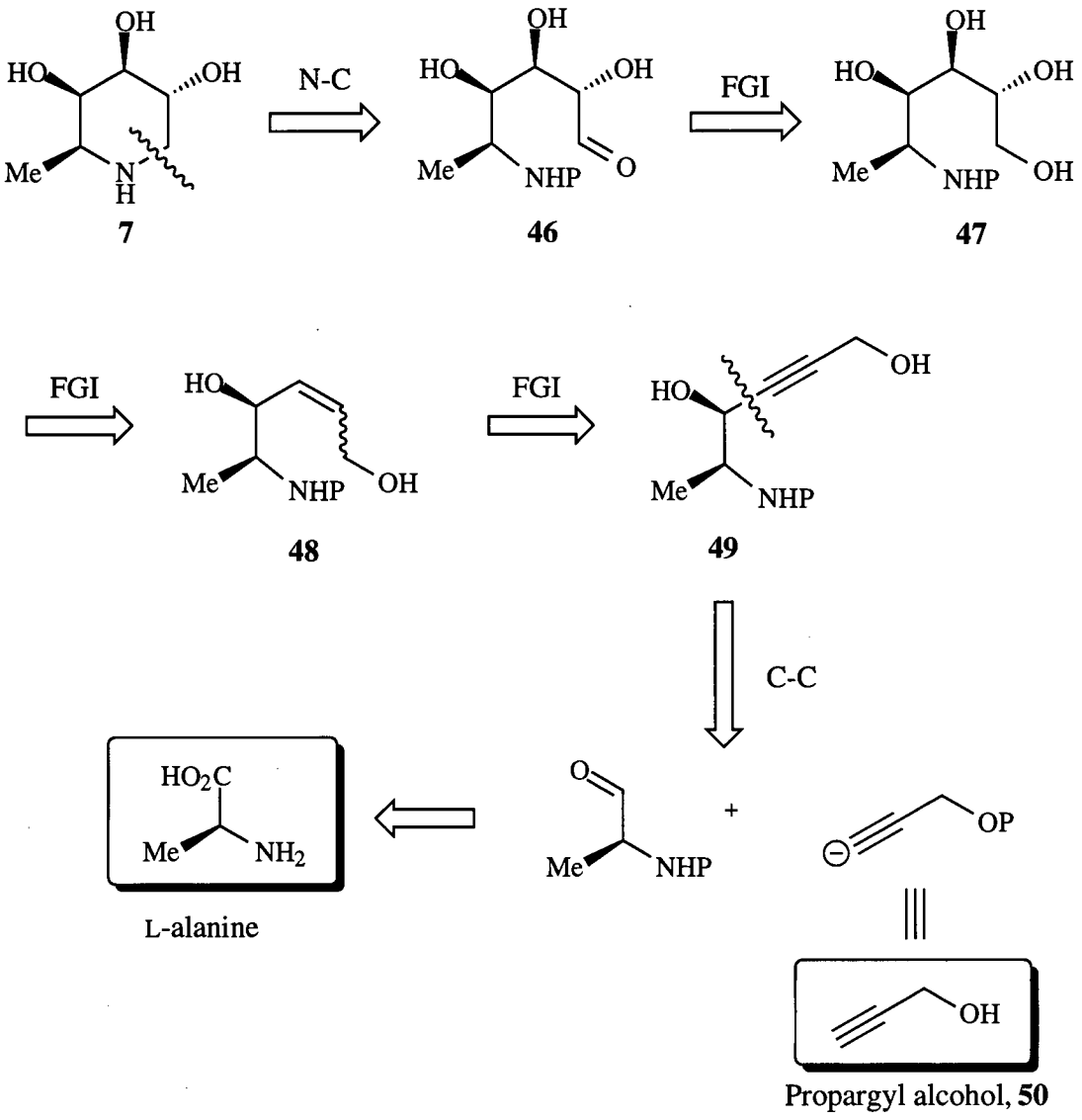
Despite the previous syntheses of DFJ[26,36] the project aim was to devise a route to the azasugar from simple acyclic starting materials and incorporate the stereochemistry in the synthesis. This strategy not only allows extension of the synthesis to the key target molecule **27** but also allows analogues of key intermediates and products to be synthesised with minor manipulation of the synthetic strategy, thereby providing a wide range of substrates for assay as potential inhibitors of α(1,3)-FucTs.

2.2 Retrosynthesis Of Deoxyfuconojirimycin

The presence of the amino functionality and the absolute configuration of the adjacent methyl group in both the simplified azasugar **7**, and the ultimate target **27**, suggested the use of the natural amino acid L-alanine **50** as a precursor. A retrosynthetic analysis of **7** is illustrated in Scheme 18.

The initial disconnection of the N-C_6 bond reveals an amino aldehyde **46** which is anticipated to undergo nucleophilic attack by the nitrogen followed by reduction to produce the piperidine ring **7**. Three functional group interconversions from the aldehyde **46** leads to the acetylene **49** *via* a triol **47** and allylic alcohol **48**. Disconnection of the C_3-C_4 bond in **49** reveals two fragments, an α-amino aldehyde and a propargylic anion, both readily accessible from L-alanine and propargyl alcohol respectively.

Scheme 18


OH
HO
OH
Me
N
H
7
N-C
OH
HO
OH
Me
NHP
O
46
FGI
OH
HO
OH
Me
NHP
OH
47
FGI
HO
Me
NHP
OH
48
FGI
OH
HO
Me
NHP
49
C-C
HO2C
Me
NH2
L-alanine
O
Me
NHP
+
OP
OH
Propargyl alcohol, 50

3. SYNTHESIS OF DEOXYFUCONOJIRIMYCIN

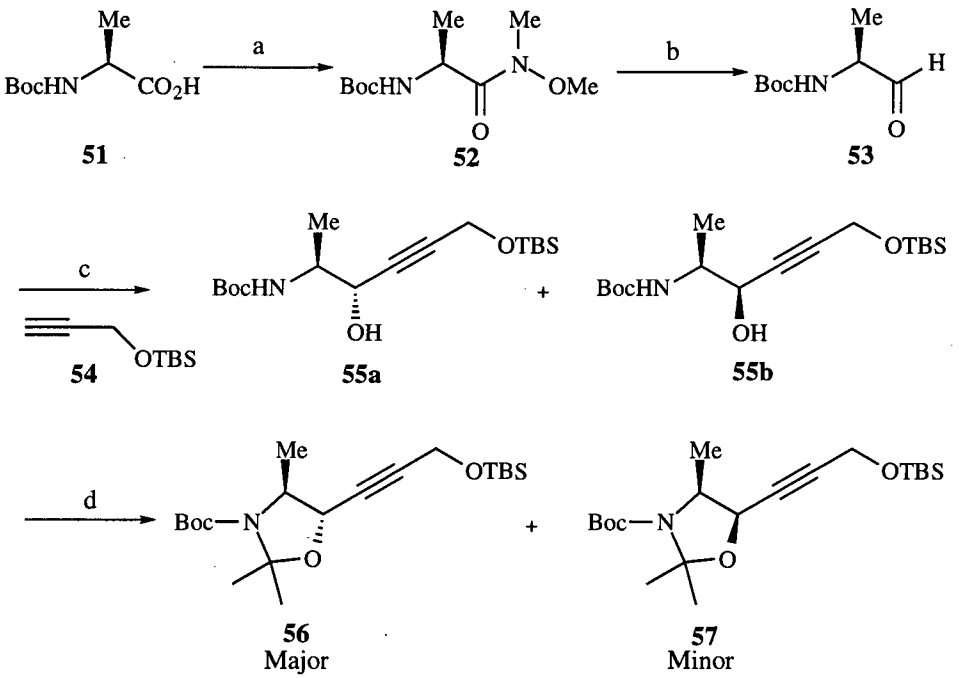
Work on the approach to DFJ from an acyclic precursor had commenced[68] in the latter months of doctorate research by Richard Cameron at the University of Exeter. As illustrated in section 3.1, despite success with the initial steps, problems were encountered later on and the route was not completed. The initial task in this body of research was to repeat and scale up the steps already implemented and continue with the synthesis of DFJ.

3.1 CONTINUATION OF ONGOING RESEARCH

3.1.1 Chiral induction of the second stereocentre

The precursor used for this synthesis was the readily available *N-tert*-butoxycarbonyl-L-alanine (*N*-Boc-L-alanine) **51** and the strategy is outlined in Scheme 19.

Scheme 19

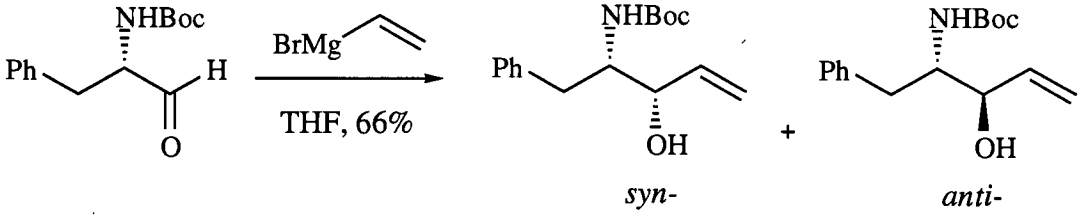


Reagents and conditions: (a) MeONHMe.HCl, *N*-methyl piperidine, MeOCOCl, DCM, -42°C→r.t., 78%. (b) $LiAlH_4$, THF, ether, -65°C, 82%. (c) **54**, MeMgI, ether, -78°C, 62%. (d) 2,2-DMP, $BF_3.OEt_2$, acetone, 68%

The aldehyde *N*-Boc-L-alaninal **53** was prepared by adaptation of a literature method by Goel *et al.*[69] This procedure involved formation of the *N*-methyl-*N*-methoxy amide **52** (known as a Weinreb amide) by initial activation of the amino acid **51** with methyl chloroformate followed by displacement of the mixed anhydride with *N,O*-dimethylhydroxylamine. Reduction of the Weinreb amide **52** to the α-amino aldehyde **53** was effected using lithium aluminium hydride in THF/ether in 82% yield and both compounds **51** and **52** were consistent with reported literature.[70]

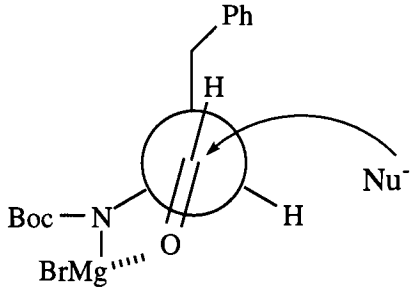
Preparation of the *tert*-butyldimethylsilyl ether **54** was achieved by treatment of the readily available propargyl alcohol **50** with *tert*-butyldimethylsilyl chloride and catalytic imidazole in pyridine. The addition of the acetylene **54** to the α-amino aldehyde **53** was adapted from a procedure by Hanson and Lindberg[71] who reported the addition of vinylmagnesium bromide to *N*-Boc-L-phenylalaninal resulting in a mixture of allylic alcohols *syn-* and *anti-*, (Figure 26).

Figure 26



At -78°C in THF, a mixture of *syn-* and *anti-* were obtained in a ratio 56:44 respectively and in a yield of 66%. An improvement in selectivity was observed in favour of the Cram-chelation controlled product (*syn*) on performing the reaction at room temperature. At the higher temperature it was proposed that a higher proportion of NH protons would be removed to form the Cram-transition state as shown in Figure 27 prior to the aldehyde carbonyl addition, resulting in preferential formation of *syn*-isomer in a ratio 70:30.

Figure 27

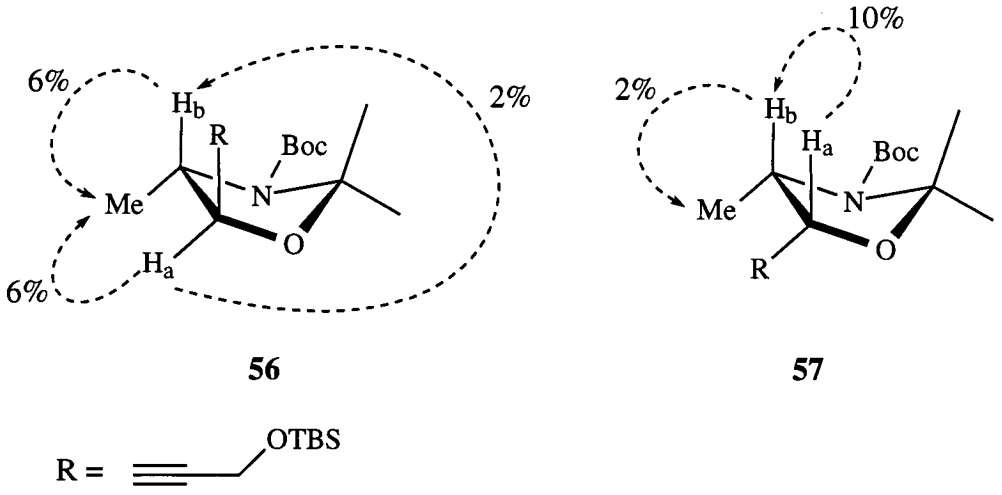


Application of this methodology to favour formation of the desired amino alcohol **55a** was implemented. Initially the corresponding Grignard reagent of the acetylene **54** was prepared (MeMgI, ether, reflux) and 2 equivalents added to *N*-Boc-L-alaninal **53** at low temperature resulting in an inseparable mixture of β-amino alcohols **55a/b** (62%). The ratio of diastereomers was relatively low (2:1) as determined by the ratio of the α-methyl signals in the ^{1}H nmr spectrum and very little difference in selectivity was observed by repeating the reaction at room temperature. As a consequence, the reaction was subsequently performed at low temperature to avoid any possible racemisation and unwanted side products. In addition, the reaction was carried out in ether rather than THF due to the insolubility of the *in situ* generated Grignard reagent of **54** in THF.

Previous attempts to improve this ratio of diastereomers in favour of the amino alcohol **55a** by using other acetylene additions or asymmetric reductions of a chiral α,β-acetylenic ketone failed to provide an improved system.[68]

Separation of the β-amino alcohols **55a/b** was achieved by formation of the corresponding oxazolidines **56** and **57** (2,2-DMP, $BF_3.OEt_2$, acetone[72]) and column chromatography. ^{1}H nmr nOe experiments were performed on both the oxazolidines to verify the stereochemistry of the newly formed stereocentres and the results are illustrated in Figure 28.

Figure 28



56 **57**

R =

The nOe enhancements, which result from through space interactions, suggest that the protons H_a and H_b in the oxazolidine **56** are *anti-* to each other due to the small percentage enhancement (2%) observed compared to that in oxazolidine **57** (10%).

Further evidence for the *anti*- relationship in **56** is depicted between H_a and Me where an enhancement of 6% was observed while in the diastereomer **57** no enhancement was recorded due to the distance between the relative groups.

Using the methodology developed by Cameron[68] the above reactions were performed with the yields quoted. A considerable amount of time was spent in the early months of this project scaling up these initial 4 steps and as a result, all have been performed successfully on a large scale ranging from 15-25g of substrate in acceptable yields. The only obstacle encountered in the scale up was the time consuming separation of the oxazolidine diastereomers **56** and **57**, which required several column chromatography steps in order to obtain pure product.

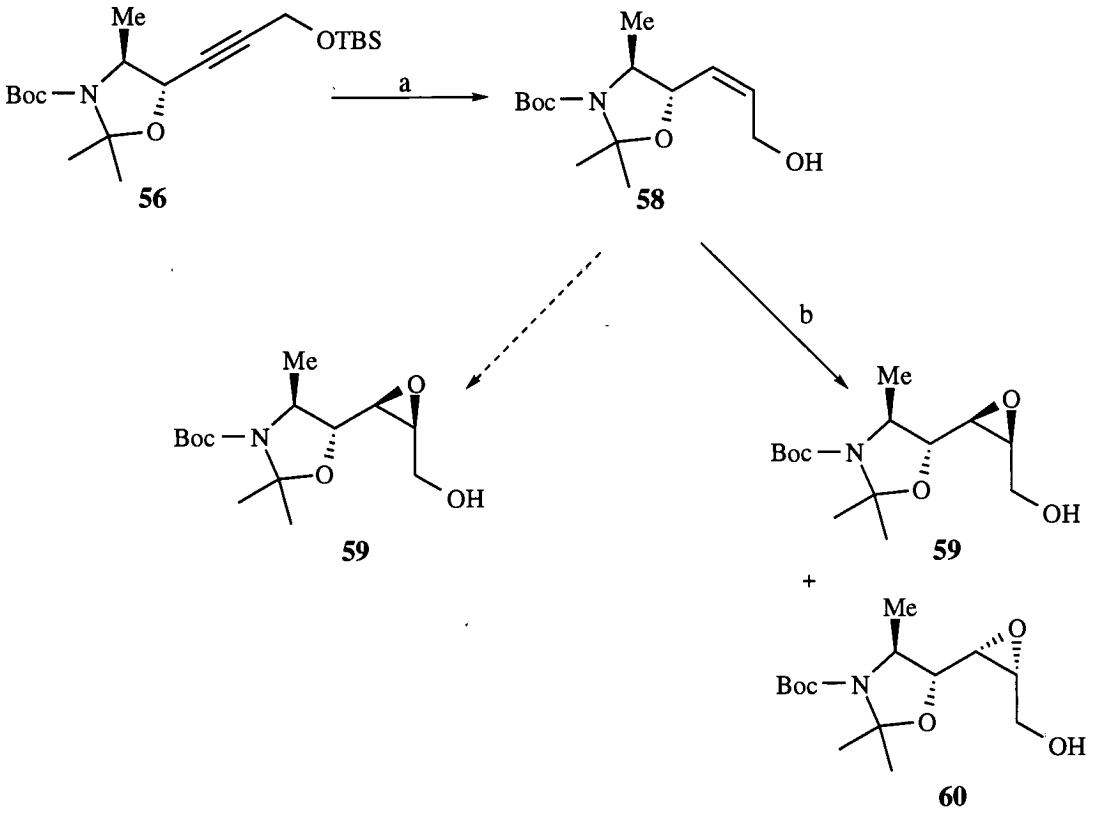
3.1.2 Introduction of the hydroxyl functionality

The next steps in the proposed route to DFJ **7** required the introduction of two hydroxyl groups into the major oxazolidine **56** which already contained two of the required four stereocentres. This route was still that initially performed by Cameron and it was along this pathway that problems were encountered.

Reduction of the acetylene function of **56** to the *Z*-alkene was achieved under hydrogenation conditions in the presence of the Lindlar catalyst. Although Cameron reported the need for quinoline as a poison to prevent any over reduction, it was found that there was no need for this additive as the reaction proceeded in excellent yields (>90%) with no observed side products. Removal of the silyl protecting group was achieved under standard conditions of tetrabutylammonium fluoride in THF to give the *Z*-allylic alcohol **58**, (Scheme 20).

It was envisaged that epoxidation of the *Z*-alkene and epoxide ring opening would allow the two hydroxyl groups to be introduced but initial attempts by Cameron to epoxidise the *Z*-alkene **58** asymmetrically utilising the Sharpless epoxidation conditions failed to give any significant amount of desired product **59** after 3 weeks (10-20%). Further attempts using *meta*-chloroperbenzoic acid gave epoxides **59** and **60** in an overall yield of 78% after 6 days but with no selectivity of epoxide formation.[68] It was evident from an attempt at this same reaction in this project, that the epoxidation was indeed slow due to the slow depletion of the starting material when monitored by tlc after 3 days, hence the reaction was abandoned. This slow rate of reaction was attributed to the electron deficient nature of the alkene.

Scheme 20



Reagents and conditions: (a) i. Lindlar catalyst (Pd on $CaCO_3$), H_2, hexane, 94%. ii, TBAF, THF, 77%. (b) *m*CPBA, DCM.

3.1.3 Conclusion

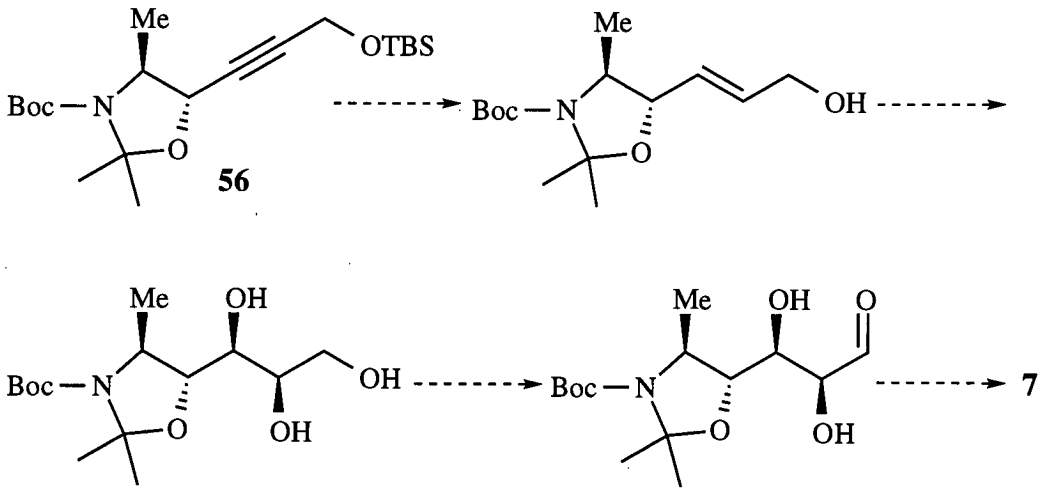
Although this route to DFJ showed potential in the early stages, the low selectivity and yield of the epoxidation prevented continuation of this synthetic pathway. As a result a new route was undertaken to introduce the remaining stereochemistry.

3.2 Revised Approach To Deoxyfuconojirimycin

To utilise some of the methodology already developed in the previous synthesis, it was anticipated that introduction of the two remaining stereocentres could be effected *via* formation of the *E*-alkene from the oxazolidine **56**, which would then align the system for a *syn*-dihydroxylation. The product from this strategy would include all the

functionality required and ring cyclisation could then be effected to produce DFJ **7**. Scheme 21 illustrates the proposed route.

Scheme 21



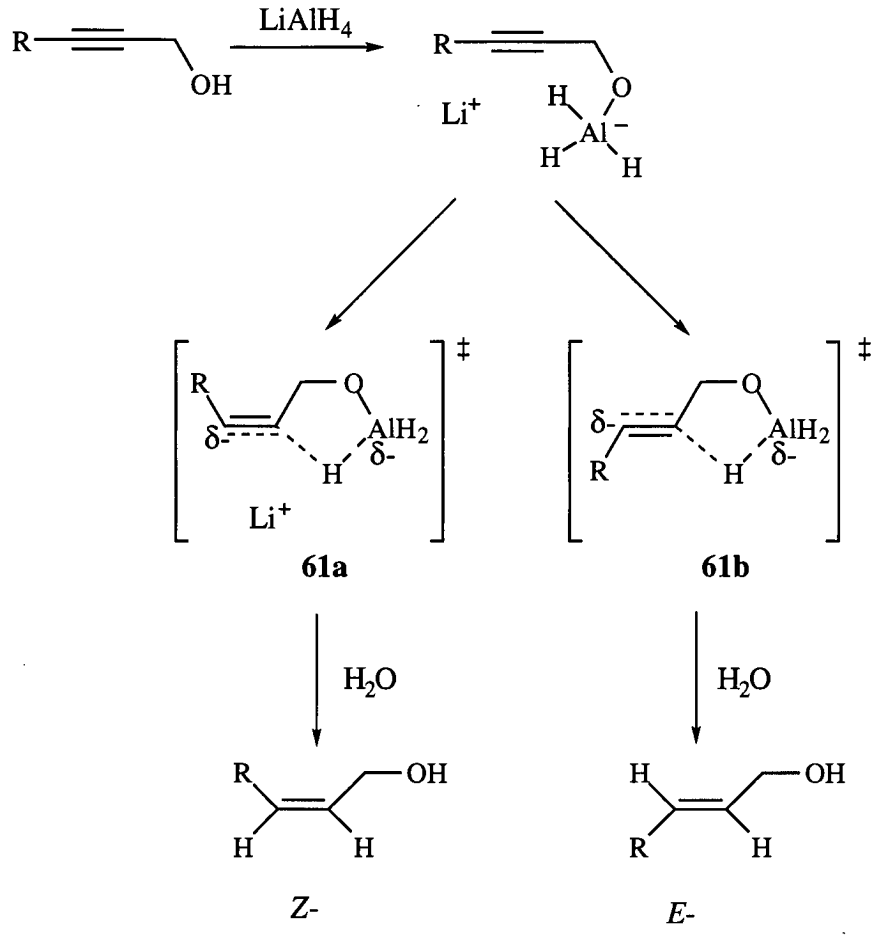
3.2.1 Acetylene reduction to an *E*-allylic alcohol

There are several ways of reducing acetylenes to *E*-alkenes[73] among which are dissolving metal reductions-sodium/liquid ammonia,[74] use of low valent transition metal ions such as chromium sulfate[75] and use of hydride reducing agents.

The mechanism of hydride reduction of simple propargylic alcohols has been reported by Grant and Djerassi using lithium aluminium hydride.[76] These results illustrated that reduction of the propargyl alcohols in THF gave essentially products due to *E*-reduction, but in ether a second product was often isolated and identified as the *Z*-alkene. Grant and Djerassi proposed a mechanism for the two solvent dependent pathways for the reduction under these conditions and this is shown in Figure 29.

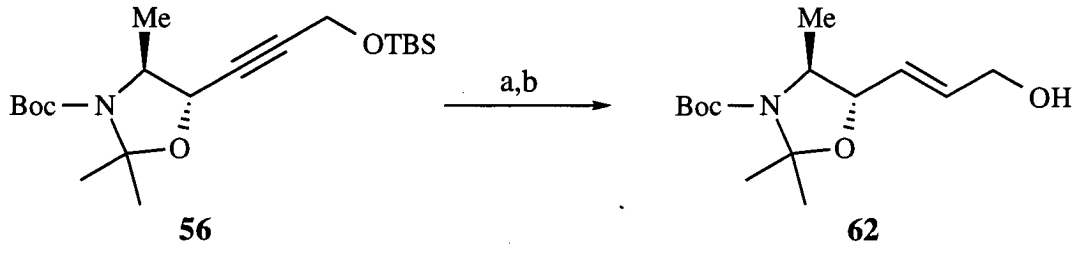
After formation of the O-Al bond, intramolecular hydrogen transfer occurs resulting in the formation of the transition states **61a** or **61b**. In weak Lewis basic solvents like ether, the lithium counter ion is readily available to stabilise the developing anionic charge in the transition state **61a**. In the strong Lewis basic solvent THF, the developing anionic centre would not be stabilised by the lithium counter ions due to solvation and would result in an energetically favoured configuration with the greatest charge separation, as depicted in **61b**. Hydrolysis of these transition states would then occur with retention of configuration to give the *Z*- and *E*-isomers, respectively.

Figure 29



To apply this methodology, the silyl protecting group in the oxazolidine **56** was cleaved under standard conditions (TBAF, THF) and the resulting propargylic alcohol subjected to lithium aluminium hydride reduction in THF (Scheme 22).

Scheme 22



Reagents and conditions: (a) TBAF, THF, 90%. (b) $LiAlH_4$, THF, -78°C, 90%.

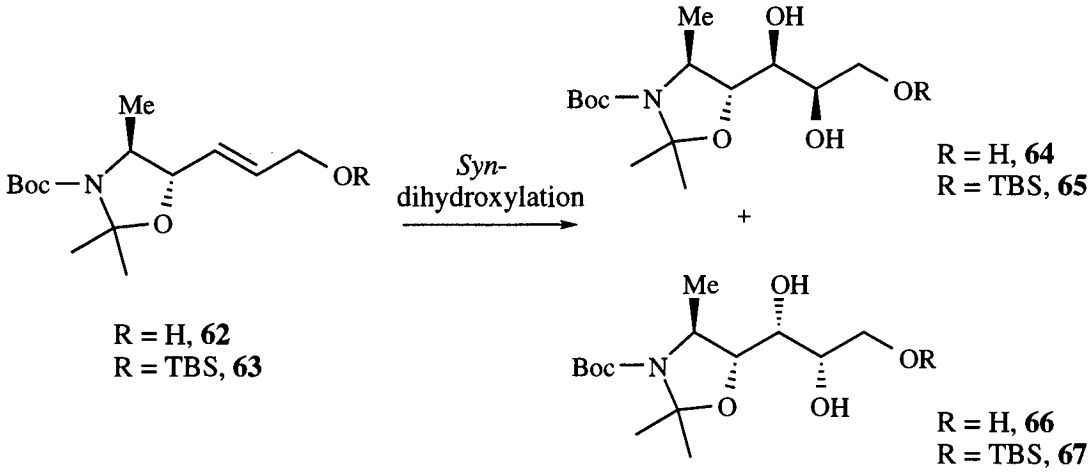
Verification of *E*-alkene formation was obtained from the ^1H nmr spectrum which revealed the alkene protons in the region δ 5-6 with characteristic coupling patterns and vicinal coupling of *J* 15.5 Hz. As initially predicted no *Z*-alkene was observed and in

addition no products resulting from attack of the hydride reagent at the carbonyl of the *N*-Boc group was observed.

3.2.2 *Syn*-dihydroxylation

A stereoselective *syn*-dihydroxylation of the *E*-alkene was envisaged to introduce the two remaining hydroxyl groups as illustrated in Scheme 23.

Scheme 23



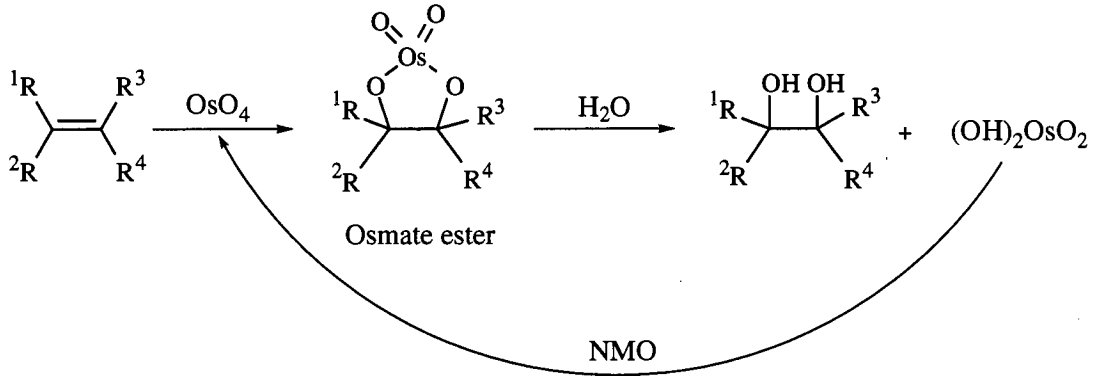
Top face attack of the reagent on the *E*-alkene **62** or **63** is required to give the diol with the appropriate stereochemistry for DFJ (**64** or **65**). Several attempts at this step were performed and the outcome is outlined below.

3.2.2.1 Use of catalytic osmium tetraoxide

The reaction of osmium tetraoxide (OsO_4) with an alkene is undoubtedly the most reliable method for a *syn*-dihydroxylation of the double bond and has been used extensively throughout organic chemistry for many years. At the turn of the century it was discovered that osmium tetraoxide could be used catalytically in the presence of a secondary oxygen donor such as sodium chlorite avoiding the use of osmium tetraoxide in stoichiometric quantities which is impractical due to its high cost and toxicity. Since then several other oxidising agents have been used in conjunction with osmium tetraoxide for the catalytic oxidation of alkenes, and these include hydrogen peroxide, sodium hypochlorite, and one of the most used to date, *N*-methyl-morpholine-*N*-oxide[77] (NMO).

The overall result of OsO_4 addition to an alkene in the presence of NMO is shown in Figure 30. The osmium tetraoxide adds to the alkene to form an osmate ester species which then undergoes hydrolytic cleavage of the Os-O bonds to yield the *syn*-diol. Regeneration of the osmium tetraoxide occurs by oxidation of the osmic acid formed in the hydrolysis, by the co-oxidant. Due to the large steric requirements of the osmium, reactions take place predominately from the least hindered side of the double bond.

Figure 30



Osmylation of the allylic alcohol **62**

Treatment of the *E*-allylic alcohol **62** under the conditions of catalytic osmylation in acetone/water with NMO gave a mixture of diastereomers **64** and **66** in a combined yield of 84%. The ratio of diastereomers was determined by comparison of the integral intensities of the oxazolidine methyl doublets (δ 1.3) in the ^1H nmr spectrum, and suggested a ratio of 3:1. Separation by column chromatography gave the diastereomers **64** and **66** in a similar ratio.

Two key factors allowed tentative assignment of the major triol. The initial factor takes into consideration the bulky osmium reagent which with the alkene **62** adds to the top face of the alkene due to steric crowding of the lower face, and the second factor is based on studies performed by Kishi and co-workers[78] One of the conclusions resulting from Kishi's research stated that *"the relative stereochemistry between the pre-existing hydroxyl or alkoxy group and the adjacent newly introduced hydroxyl group of the major product in all cases is erythro"*. Consequently, it was predicted that the major diastereomer formed from osmylation of the alkene **62** is the triol **64**.

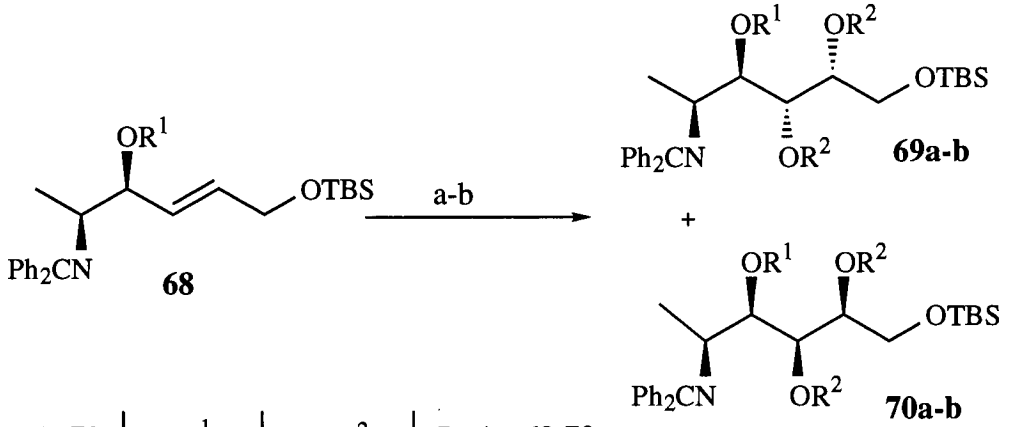
Although the ratio of diastereomers **64**:**66** was low, it was not unexpected and correlated well to experimental results reported by Kishi. On the basis of these same results by Kishi it was anticipated that an improvement in the ratio may have been

possible through use of stoichiometric osmylation conditions, however the high toxicity and cost of this reagent far outweighed its use for a slight improvement in diastereomer ratio.

Osmylation of the *E*-alkene **63**

An attempt to improve on the selectivity produced in the osmylation of alkene **62** was undertaken after a recently published report by Sames and Polt[55] illustrated two dihydroxylation procedures *en route* to DFJ **7**, both of which are outlined in Figure 31. The stereochemical outcome was as that predicted by Kishi[78], however the diastereoselectivity of the products looked very promising with reported ratios ranging from 6:1 for the allylic alcohol (R^1=H) to 10:1 for the ester (R^1=Pivaloyl).

Figure 31



69,70	R^1	R^2	Ratio, **69:70**
a	H	Ac	6:1
b	Piv	MOM	10:1

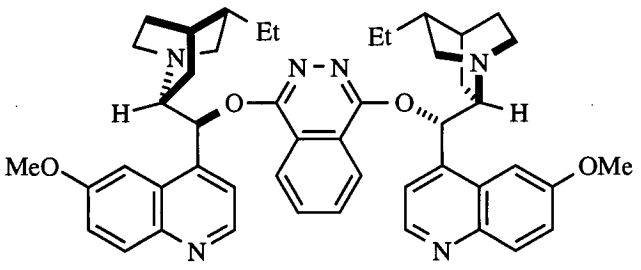
Reagents and conditions: (a) $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, ^tBuOH, H_2O. (b) Ac_2O, pyridine or MOMCl, pyridine.

Hence, the allylic alcohol **62** was initially protected by treatment with *tert*-butyldimethylsilyl chloride and imidazole/DMF to furnish the TBS-ether **63** and then subjected to the conditions used by Polt. Unfortunately, both the diastereomers **65** and **67** were again obtained in a ratio of 3:1 and combined yield of 77%, therefore showing no improvement from osymlation of the allylic alcohol **62**.

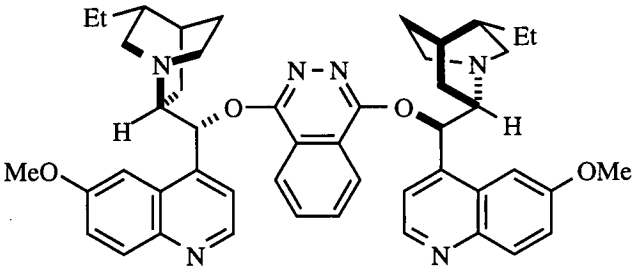
3.2.2.2 Osmium catalysed asymmetric dihydroxylation (AD)

An attempt to asymetrically dihydroxylate the *E*-alkene **62** was undertaken using the Sharpless asymmetric dihydroxylation procedure involving the use of AD-mixes.[79-81] These pre-mixed formulations contain 0.2 mol% $K_2OsO_2(OH)_4$ as a non-volatile source of OsO_4, 3 mole equivalent of co-oxidant $K_3Fe(CN)_6$ and K_2CO_3, and 1 mol% of the chiral ligand. The two mixes known as AD-mix-α and AD-mix-β differ in formulation only by the type of ligand present, i.e. $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL respectively

Figure 32



$(DHQD)_2$-PHAL



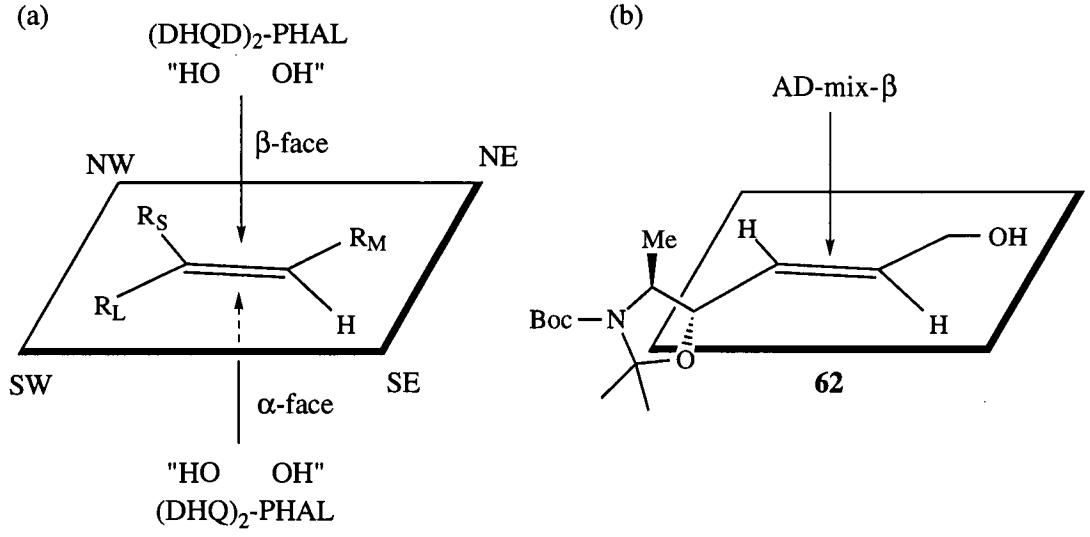
$(DHQ)_2$-PHAL

A mnemonic device for predicting the enantiofacial selectivity in the reaction has been derived from extensive studies and is shown in Figure 33a. In this mnemonic device, the southeast quadrant and northwest (to a lesser extent) present steric barriers but the northeast is relatively open for olefin substituents of moderate size. The southwest quadrant is regarded as being an 'attractive' site - well suited to accommodate flat, aromatic substituents or large aliphatic groups.

Asymmetric dihydroxylation of the *E*-alkene **62** represents a 'double asymmetric synthesis' which concerns the interaction of two homochiral reactants, the substrate and reagent. For olefins with an allylic heteroatom it can be predicted which combination of reagents will constitute a "matched" or "mismatched" pair by

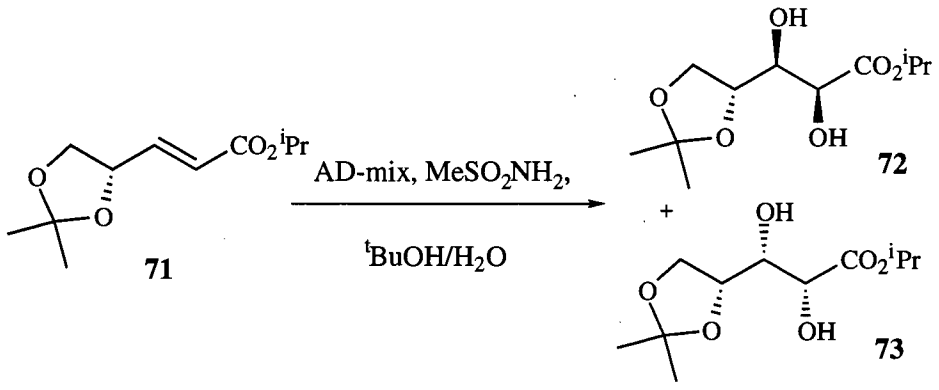
employing the mnemonic device in conjunction with the Kishi[78] rules. As a result, it was predicted that use of the AD-mix-β containing the $(DHQD)_2$-PHAL as chiral ligand to give the preferred diol **64** should constitute a matched pair, (Figure 33b).

Figure 33



A representative example of a double diastereoselection of an olefin reported by Morikawa and Sharpless[82] is shown in Figure 34. In the matched case, the phthalazine ligand $(DHQD)_2$-PHAL gave the diastereomers **72** and **73** in a ratio of 39:1 respectively, and in the mismatched case with ligand $(DHQ)_2$-PHAL a ratio of 1:1.3 respectively was obtained. Both these results were obtained with use of the standard AD-mix conditions, hence these conditions were applied to the *E*-alkene **62** in the anticipation of obtaining an improved ratio of diastereomers in favour of the triol **64**.

Figure 34



Alkene **62** was treated with the AD-mix-β[81] and 1 mole equivalent of methane sulfonamide in *tert*-butanol/water at 0°C for 10 hours then at room temperature for a further 24 hours. Monitoring the reaction by tlc gave early indications of product

formation but little difference after 34 hours. Work up followed by column chromatography gave recovered starting material and product **64/66** (20%), and ^{1}H nmr spectrum unfortunately suggested a ratio of the diastereomers (3:1) similar to that achieved by the catalytic osmylation conditions without the ligand.

This was disappointing due to above literature precedent, but it was noted that other examples of double diastereoselectivity[79,80] used quantities of potassium osmate and chiral ligand exceeding that in the commercial AD-mix. It was suggested that chelation of substrate substituents to the osmate (VI) ester may cause suppression of the reaction, but an increase in both reagent concentrations alleviated this problem. This increase in ligand and osmium concentration is referred to as the "Super AD-mix".

Despite this literature precedent the super AD-mix was not utilised on the *E*-alkene **62** as it was anticipated that only the rate of reaction would be increased and not necessarily the diastereoselection due to a possible incompatibility of the substrate and the chiral osmium species in the reaction.

3.2.2.3 Use of catalytic ruthenium tetraoxide

Ruthenium tetraoxide (RuO_4) has been used as an oxidant for many organic transformations such as oxidative fissions of olefins to give carbonyl compounds, acetylenes to give 1,2-diketones and for the oxidation of primary alcohols.

Dihydroxylation of olefins to *syn*-diols with catalytic ruthenium tetraoxide was observed to proceed in a biphasic solvent system of ethyl acetate, acetonitrile and water (ratio 3:3:1). In the presence of 0.07 mole equivalent $RuCl_3.(H_2O)_3$ and 1.5 mole equivalent of sodium periodate (*in situ* generation of RuO_4) *syn*-dihydroxylation occurred within minutes with only minor products due to oxidative fission of the alkene.[83,84] Treatment of the *E*-alkene **62** under the conditions reported by Shing, followed by rapid quenching of the reaction mixture after 3 minutes gave recovered starting material and product (30%). ^{1}H nmr analysis of the diastereomeric triol mixture again suggested a ratio of **64** and **66** of 3:1, hence showing no improvement. A minor product was also isolated from the reaction mixture and this indicated that oxidation of the primary alcohol in **62** had occurred resulting in an α-β-unsaturated aldehyde.

3.2.2.4 Summary of the *syn*-dihydroxylation

The best overall process of the *syn*-dihydroxylation of the *E*-alkene **62** resulted from the use of catalytic osmium tetraoxide with NMO as co-oxidant in acetone and water. This reaction has been performed on a scale ranging from 0.1g - 2.6g of alkene with very little difference in the yield obtained, and in most cases more than the required 1 mol% of osmium tetraoxide was used due to the difficulties in handling and weighing such small quantities of the reagent.

The osmylation reaction on the silyl protected alcohol **63** by *in situ* generation of the osmium tetraoxide with the use of the co-oxidant potassium ferricyanide showed no advantage over that of the above case, and use of ruthenium tetraoxide on alkene **62** gave low yield of product with no increase in selectivity and also indicated the presence of undesired side products.

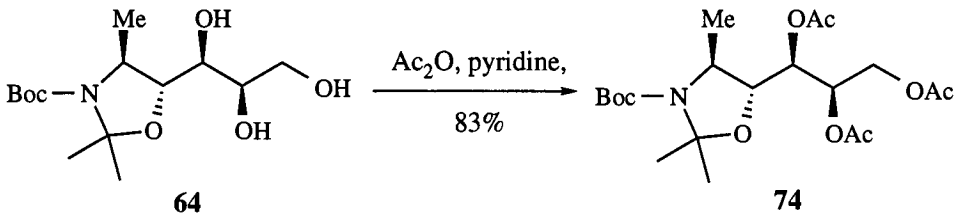
Improvements on the asymmetric dihydroxylation using the AD-mixes could have been attempted by employing different temperature or allylic alcohol protecting groups, and also by repeating the reaction with the AD-mix-α for comparison. However, due to the amount of time spent on this reaction step as a whole it was decided not to implement these but to continue the synthesis.

Additional points

The high field ^{1}H nmr spectrum of the major triol diastereomer **64** was improved by simply changing from deuterated chloroform ($CDCl_3$) to deuterated methanol (CD_3OD). Broad signals observed in $CDCl_3$ were much sharper in CD_3OD and coupling patterns were very clear. As a result full assignment of all signals was achieved aided by a ^{1}H-^{13}C correlation spectrum. Attempts to improve the broad and complex spectra of the minor triol **66** in a similar manner failed due to insolubility of the isomer in CD_3OD, and also decomposition of the isomer when left at room temperature overnight or after being dissolved in solvent for any period of time. Significantly less decomposition was observed for the major diastereomer **64** under similar conditions.

The major diastereomer **64** was also subjected to acetylation conditions (Ac_2O, pyridine) to verify triol formation and aid in the characterisation of the compound, (Scheme 24).

Scheme 24



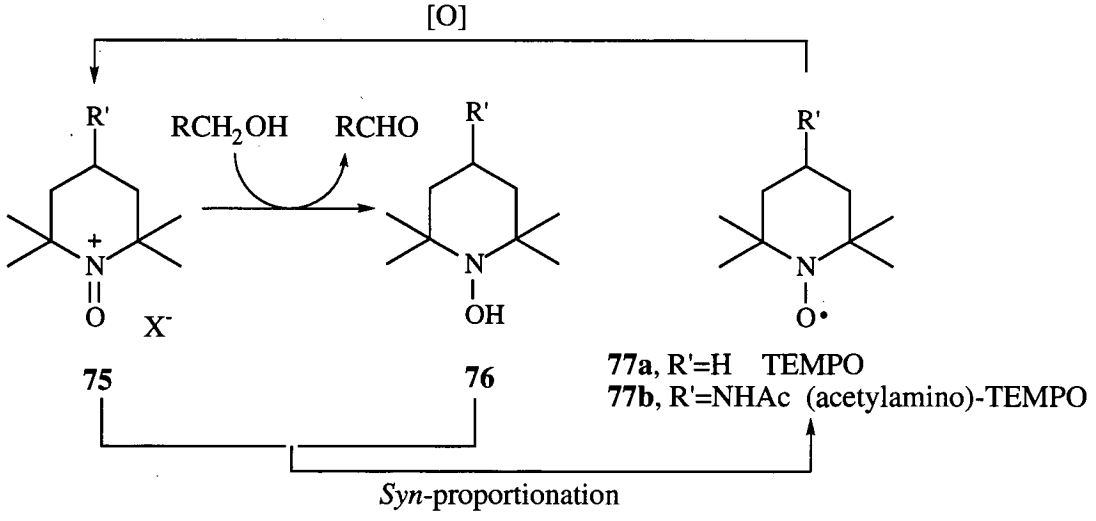
Clean formation of the acetylated triol **74** was achieved and full data analysis obtained.

3.2.3 Selective oxidation of a primary alcohol

There are very few efficient methods for the selective oxidation of primary alcohols over secondary alcohols.[85,86]

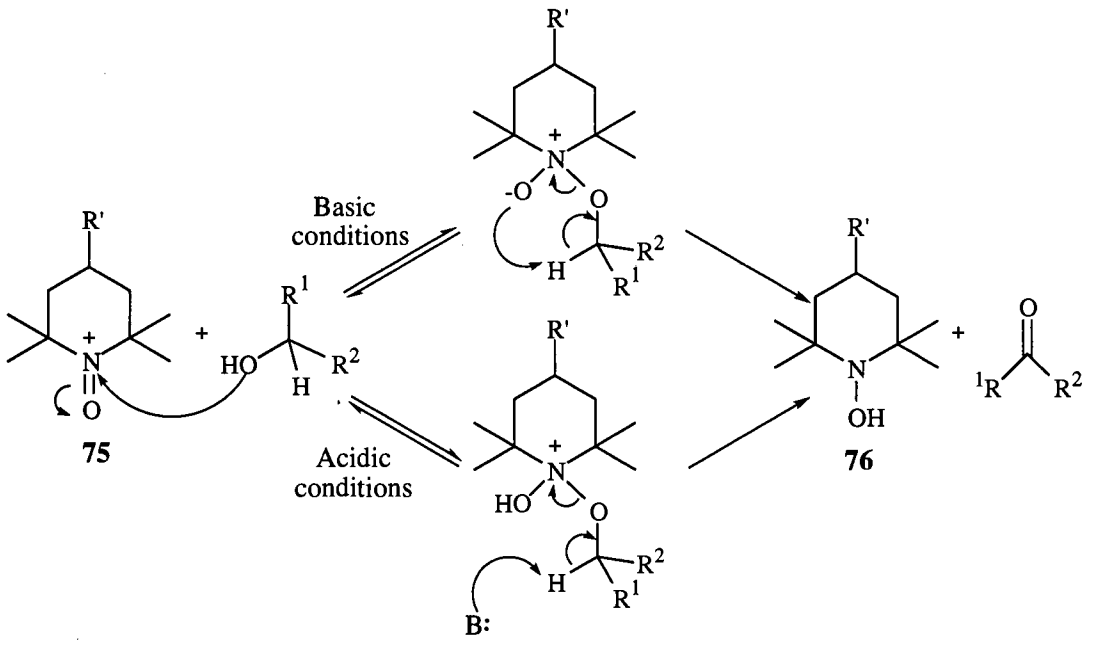
TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy, **77a**) a nitroxyl radical species, has emerged as a mild oxidant used catalytically with bleach as co-oxidant. Semmelhack[87] proposed that the oxoammonium salt **75** reacts with alcohols forming the corresponding carbonyl compound and hydroxylamine **76**. *Syn*-proportionation between **75** and **76** affords two molecules of nitroxyl **77a**, which is then oxidised back to **75** to repeat the process, (Figure 35).

Figure 35



Two different pathways under basic and acidic conditions for the TEMPO mediated oxidation have been suggested,[88,89] (Figure 36).

Figure 36

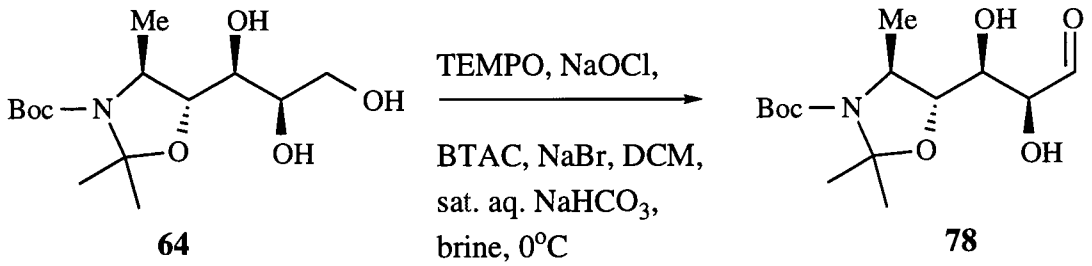


The basic reaction conditions consist of 1 mol% TEMPO **77a**, 10 mol% potassium bromide and 5 mol% of a phase transfer catalyst in a bi-phasic mixture of DCM-sat.aq. $NaHCO_3$, followed by addition of sodium hypochlorite (30% excess) buffered at ~pH 8. The acidic conditions use *para*-toluenesulfonic acid in DCM with 2 equivalents of (acetylamino)-TEMPO **77b** as preferred oxidant due to the precipitate of the resultant hydroxylamine salt and therefore ease of work up.

There is some inconsistency in the use of TEMPO as oxidant due to the observation of some over-oxidation to the carboxylic acid, but it seems to depend highly on the reaction conditions and substrate used. Secondary alcohols can also be oxidised using TEMPO but may require longer reaction times and is also dependent on the sterical demand of the alcohol, for example in a substrate containing both a primary and secondary alcohol, the primary should be oxidised more readily unless steric factors are involved. A TEMPO mediated oxidation of such a case proved successful in the synthesis of DFJ by Sames and Polt[55] and is illustrated in Chapter 1, Scheme 13. The basic conditions used were adapted from a earlier report by Skarzewski and co-workers.[90] Under these conditions, no over-oxidation of the substrates was observed.

The selective oxidation of the primary alcohol in the triol **64** (Scheme 25) was therefore attempted using these conditions. Benzyltrimethylammonium chloride (BTAC) was used as the phase transfer catalyst and sodium bromide replaced potassium bromide.

Scheme 25



After slow addition of the buffered bleach to a vigorously stirred mixture at 0°C and continued stirring for a further 30 minutes, the bi-phasic mixture was warmed to room temperature extracted with DCM and washed with sat. aq. $NaHCO_3$. Optimised reaction conditions gave a crude product which was isolated as a solid in yields ranging from 80%-quantitative. Tlc analysis was of little use in detecting product purity due to streaking on the plate, and the ^1H nmr spectrum was unclear due to broad signals. The ^{13}C nmr spectrum was also difficult to assign due to presence of various contaminants but it was noted that the CH_2 signal of the precursor triol **64** had disappeared as would be expected. In addition, no aldehydic signal was observed but this is not uncommon in aldehydes due to oligomerisation and hydration of the carbonyl.

It was assumed aldehyde **78** resulted from the TEMPO oxidation after repetitions produced consistent results, hence the crude product was used directly in the next sequence of reactions to obtain a cyclised product.

3.2.4 Piperidine ring formation

It was anticipated that removal of the nitrogen protecting group in aldehyde **78** to give the free amine, would allow ring closure by nucleophilic attack to occur (Scheme 26). Several deprotection conditions were attempted with unexpected results.

Initially, it was proposed that a selective deprotection of the acetonide leaving the Boc protecting group intact would result in formation of the piperidine **79a**, but treatment of the crude aldehyde **78** with Amberlyst 120H in aqueous methanol[72] failed to give little more than starting material after 7 days.

Scheme 26

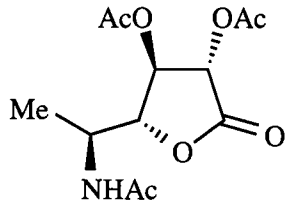
78

79a R^1=Boc, R^2,R^3=H
79b R^1=H, R^2,R^3=Ac

Treatment with aqueous trifluoroacetic acid at room temperature for 30 minutes to effect cleavage of both the Boc and acetal protecting groups gave base line material with loss of starting material when monitored by tlc. The ^{1}H nmr spectrum of the freeze dried residue was complex although there was evidence of some coupling patterns. Acetylation of this residue with acetic anhydride, DMAP and pyridine to simplify the spectra and aid characterisation of the piperidine as **79b** gave a product albeit in very little quantity (2 mg). ^{1}H nmr analysis initially looked promising with sharp coupling patterns typical of a cyclised product, but one major drawback was the observation of only three acetate signals instead of the predicted four, and a coupling pattern different to that expected for the per-acetylated fuconojirimycin **79b**. Repetition of this procedure was performed and an acetylated product similar to that previously obtained was isolated but again in small yield (6 mg after use of 100 mg of precursor **64**).

Full nmr data was obtained on this isolated product including COSY and decoupling spectra. Nominal and accurate mass spectra and infra-red data were also collected to try and assign a structure to this product which was obviously not the piperidine **79b**. As mentioned previously, only three acetate signals were present in the proton nmr, but on accumulation of the ^{13}C nmr spectrum it was noted that four carbonyl signals were present in the region δ 168-170. This was confirmed by a unidentified carbonyl stretch at 1800 cm^{-1} in the infra-red spectrum in addition to a stretch at 1752 cm^{-1} which is due to the acetate carbonyl groups.

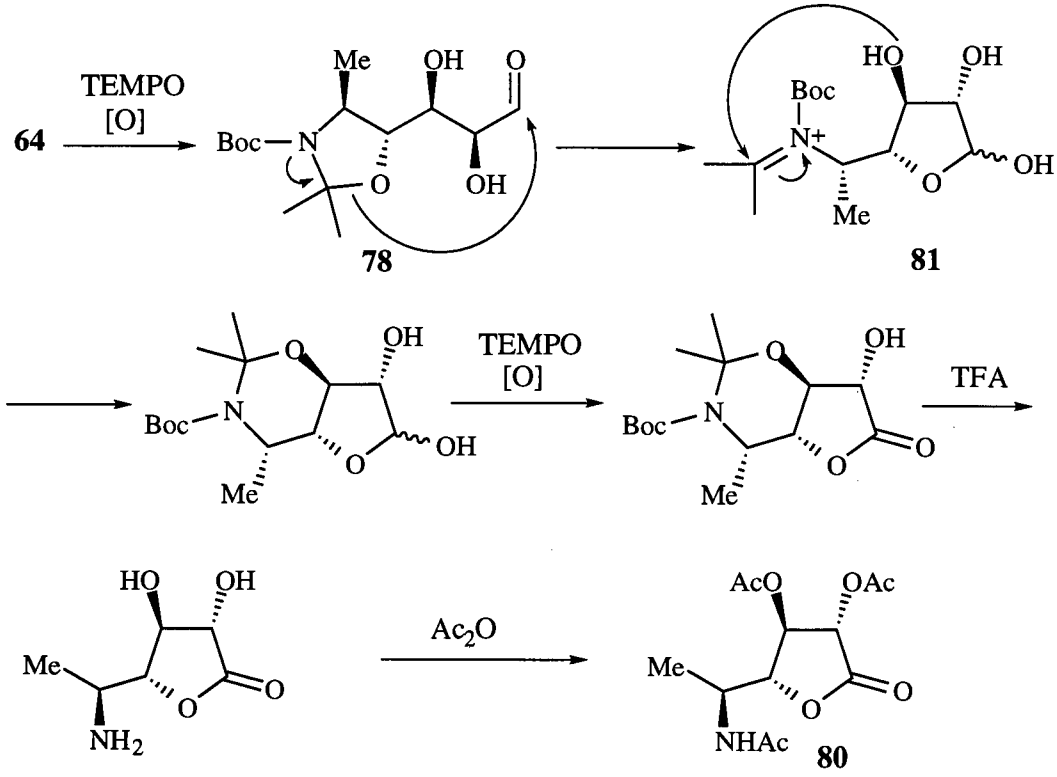
Taking into consideration all the above factors and after thorough analysis of the COSY and decoupling spectra, it was suggested that the isolated product was the lactone **80**. The structure was consistent with the accurate mass of the molcular ion (C.I.) which gave a MH^+ ion with *m/z* 288.10832 (calculated 288.10830).



80

This lactone formation was unexpected due to the literature precedent on the trifluoroacetic acid deprotection and ring closure to azasugars like nojirimycin and mannojirimycin from aldehydes,[50] hence it was proposed that the lactone may result from problems in the TEMPO-mediated oxidation. A proposed mechanism to justify lactone formation is outlined in Figure 37. The mechanism suggests that initial oxidation of the primary alcohol does occur in the TEMPO reaction but is then followed by a rearrangement resulting in the intermediate lactol **81** which contains an imine functionality which is subsequently trapped out by the secondary alcohol as indicated to give a 5-6 membered ring system. Further oxidation of this lactol produces the lactone which undergoes deprotection of the Boc and acetonide functions in trifluoroacetic acid, and acetylation to give the isolated lactone **80**.

Figure 37



Suggestions that over-oxidation of the aldehyde **78** to produce the carboxylic acid may occur in the TEMPO oxidation of triol **64** were dismissed due to several factors.

Firstly, the basic aqueous work up following the TEMPO reaction would remove any acid formed; secondly, tlc analysis did not indicate any acid formation when developed using a bromocresol blue stain which is characteristic of carboxylic acids; finally, no over oxidation was observed by Polt who utilised identical conditions, albeit on a different substrate.

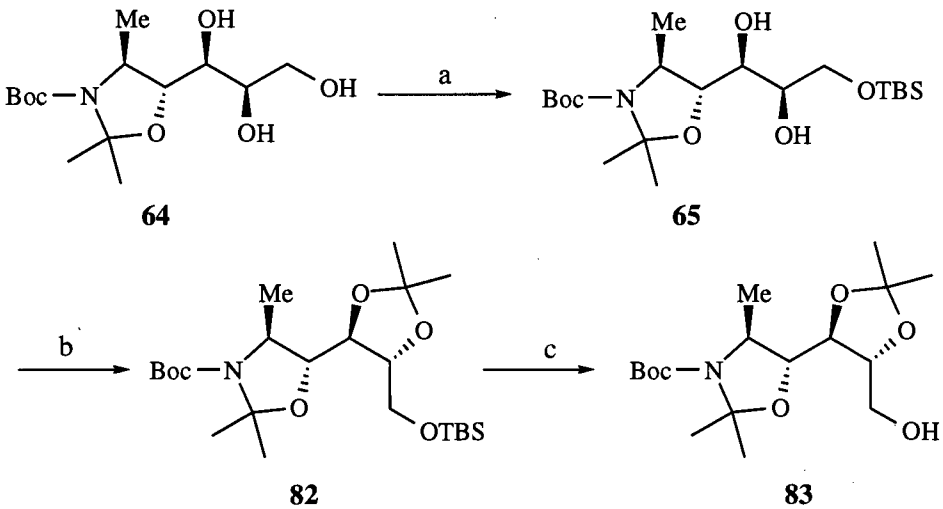
3.2.5 Route modification

From the problems encountered in the previous route due to oxidation of the primary alcohol and subsequent rearrangement involving a free secondary hydroxy group, it was anticipated that protection of the secondary hydroxyl functionality would prevent this sequence of events and result in preferential formation of the piperidine product.

3.2.5.1 Hydroxyl protection strategy

Protection of the primary alcohol functionality in triol **64** with *tert*-butyldimethylsilyl chloride in DMAP/pyridine or in imidazole/DMF failed to give the TBS-ether **65** in yields greater then 36%, however treatment with the more reactive *tert*-butyldimethylsilyl triflate and 2,6-lutidine in DCM gave **65** in good yield (75%), (Scheme 27).

Scheme 27



Reagents and conditions: (a) TBS-triflate, 2,6-lutidine, DCM, -10°C, 75%. (b) 2,2-DMP, $BF_3.OEt_2$, acetone, 85%. (c) TBAF, THF, 80%.

Protection of the two secondary alcohols as the acetonide using catalytic *para*-toluene sulfonic acid in DCM gave very little product **82**, but was effected by treatment with

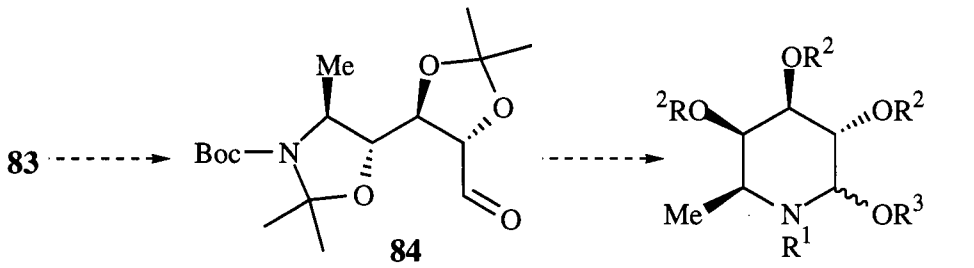
the previously used conditions for oxazolidine formation (2,2-DMP, $BF_3.OEt_2$, acetone[72]) in excellent yield. Cleavage of the silyl protecting group was achieved by use of tetrabutylammonium fluoride in THF to give the alcohol **83**, with the appropriate hydroxyl functions protected.

3.2.5.2 Alcohol oxidation and ring closure

Oxidation

Oxidation of the unprotected alcohol in the substrate **83** to the corresponding aldehyde **84** was now targeted as a precursor to a cyclised product, (Scheme 28). Several reagents were utilised in order to effect this oxidation and are outlined below.

Scheme 28

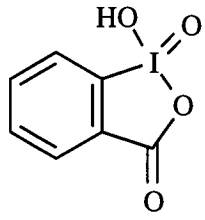


79b R^1=H, R^2,R^3=Ac
79c R^1=H, R^2,R^3=H
79d R^1=Boc, R^2=H, R^3=Me

The first reagent of choice was tetra-*n*-propylammonium perruthenate (TPAP) and was selected due to successful oxidation of alcohols by colleagues. TPAP[91,92] is a mild catalytic oxidant used in conjunction with NMO as co-oxidant and gives the corresponding carbonyls from a wide range of primary and secondary alcohols without racemisation of adjacent chiral centres. Treatment of the alcohol **83** with 5 mol% TPAP, 1.5 equivalent NMO in DCM and crushed molecular sieves gave 2 products, both very complex especially in the high field region δ 1-2 of the ^{1}H nmr spectrum and in very low yields.

An attempt using Swern oxidation conditions[93] (DMSO, oxalyl chloride, Et_3N) surprisingly gave only recovered starting material, but it was later suspected that the reagents used were of poor quality.

The third reagent to be used was the precursor to the Dess-Martin reagent, o-iodoxybenzoic acid (IBX).[94]



IBX

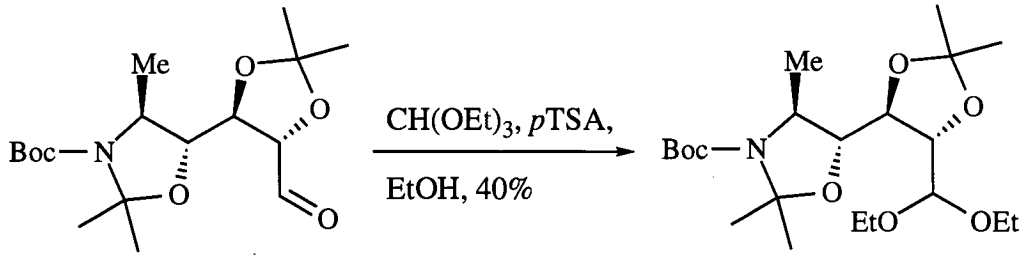
Alcohol **83** in DMSO was added to a solution of IBX in DMSO and stirred at room temperature for 48 hours before work-up. Tlc analysis indicated streaking on the plate and a crude ^{1}H nmr spectrum of the residue revealed a complex spectrum although an aldehydic proton in the low field region was observed. It also illustrated some similarities to one of the fractions obtained in the TPAP oxidation.

The oxidant that finally proved successful was the nitroxyl radical TEMPO **77a** (section 3.2.3) in which the alcohol **83** was subjected to the basic reaction conditions as employed earlier in the synthesis,[90] and monitored by tlc. Early indications showed starting material diminishing as the bleach solution was added, and after complete addition no starting material was observed. Isolation of the crude mixture was performed and subjected to nmr and mass spectral analysis. The ^{1}H nmr spectrum although complex, did show an aldehyde proton at δ 9.6 and coupling patterns in the region δ 3.5-4.5 resulting from the methine protons. The high field region δ 1-2 was complicated and indicated a high number of proton signals with respect to the lower field signals, an effect due to possible oligermerisation of the aldehyde. The ^{13}C nmr spectrum was surprisingly clear and all signals were fully assigned, including a carbonyl signal at δ 199. Aldehyde formation was also verified by infra-red spectra which showed a characteristic carbonyl stretch at 1735 cm^{-1} alongside the *tert*-butoxycarbonyl stretch at 1688 cm^{-1}.

Comparison of this ^{1}H nmr spectrum to those obtained in the TPAP and IBX oxidations showed similarities in all, but the TEMPO mediated oxidation product was significantly cleaner and higher yielding than the previous oxidations.

Derivitisation of the aldehyde **84** as the diethyl acetal **85** was achieved albeit in low yield (40%), (Scheme 29). Sufficient characterisation was obtained to reinforce the assumption that the aldehyde was formed in the TEMPO oxidation and optimisation of the conditions was not required.

Scheme 29



84 **85**

Ring closure

With conclusive evidence that aldehyde **84** had been formed, the following steps involved removal of the nitrogen protecting groups to allow the nucleophilic attack to commence.

Subjection of aldehyde **84** to 90% aqueous trifluororacetic acid[50] for 30 minutes followed by removal of the solvent under reduced pressure, was expected to give the cyclised piperidine **79c** as the free base after ion exchange chromatography. To aid identification of the product the residue was taken up in pyridine and acetylated using acetic anhydride to yield **79b**. On inspection of the ^{1}H nmr spectrum it was evident that the expected piperidine **79b** had not been formed, but a compound with proton signals resembling that of the lactone **80**. Other impurities were also present which were difficult to remove by column chromatography due to insufficient separation and streaking and as a result this compound was not characterised.

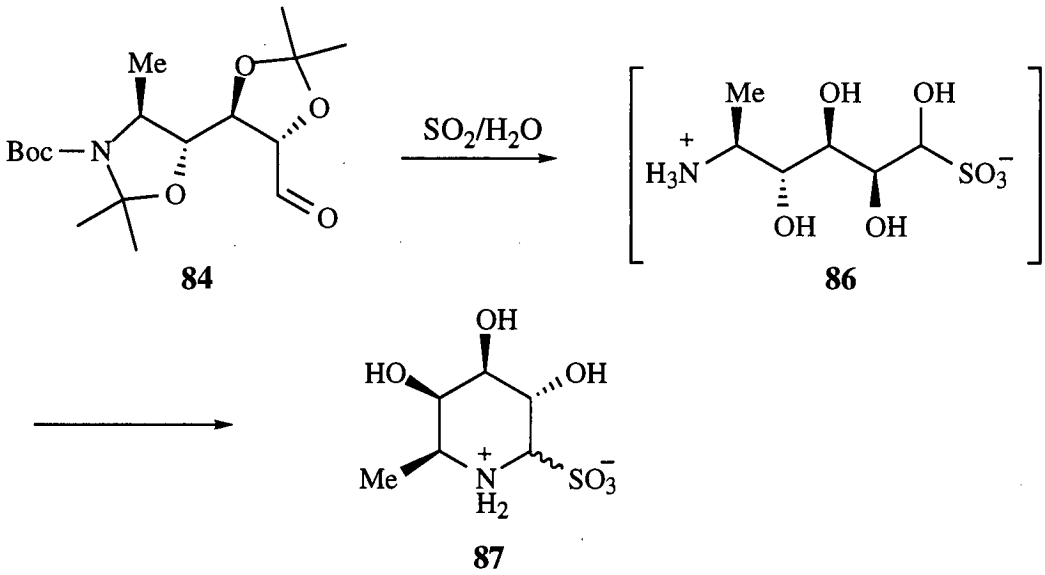
Other acidic deprotections which also were unsuccessful included *para*-toluene sulfonic acid in methanol[51] at 50°C in an attempt to form the piperidine **79d**, but resulted in a multispot mixture when monitored by tlc. Use of 1M and 3M hydrochloric acid in EtOAc in an attempt to produce **79c** resulted in crude residues that exhibited complex ^{1}H nmr spectra although did suggest cleavage of the Boc and acetal protecting groups due to the absence of these peaks. Attempts to isolate an acetylated product **79b** from one of these residues by treatment with acetic anhydride in pyridine gave a multispot mixture by tlc and as a result was not purified.

Unsuccessful formation of azasugars **79b-d** by use of the above acidic conditions resulted in an attempt to form a bisulfite adduct of the azasugar from the aldehyde **84**. There is a significant amount of literature on the formation of the bisulfite adducts *en route* to azasugars such as nojirimycin, deoxynojirimycin and mannojirimycin,[59,95-97]

and it was hoped that application of this methodology to the aldehyde **84** would prove successful.

Sulfur dioxide in water produces sulfurous acid (H_2SO_3) which was predicted to cleave the Boc and acetal groups in the aldehyde **84** to give the bisulfite adduct **87** *via* the intermediate **86**, (Scheme 30).

Scheme 30



84 **86** **87**

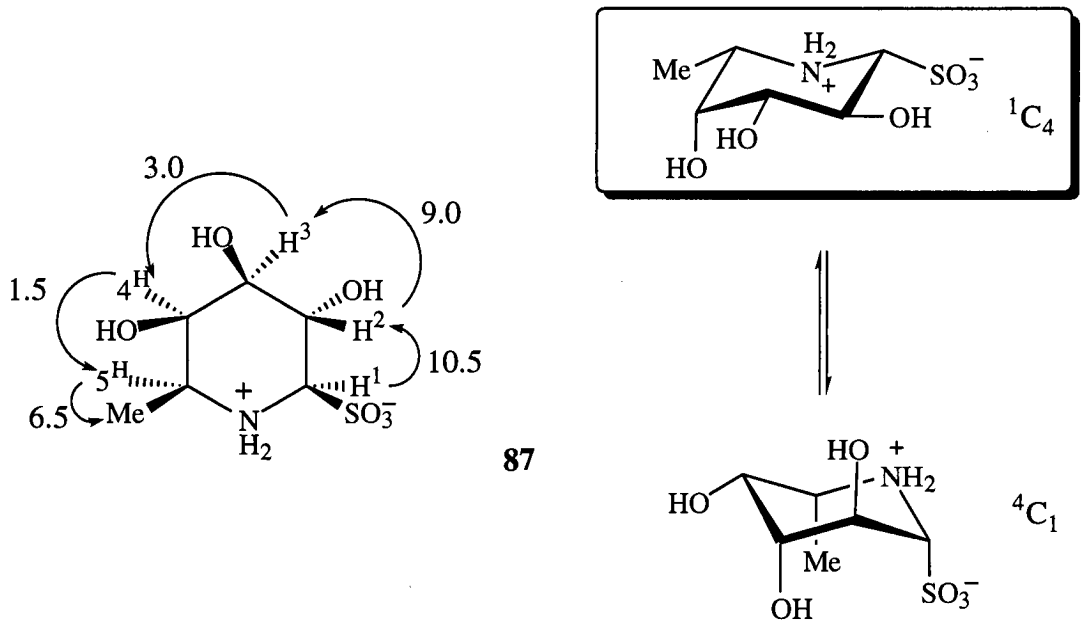
The procedure was adapted from a report by Dondoni and Perrone[51] and involved saturation of an ice-cold solution of the aldehyde **84** in water with sulfur dioxide gas and continued stirring at 40°C for 2 days. In the first trial, dilution of the mixture after 2 days with methanol and re-saturation with sulfur dioxide at 0°C failed to give any precipitate as anticipated. Removal of the solvent under reduced pressure did result in a off white solid, but the yield was very high (>100%) and the presence of more than one product was evident in the complex nmr spectra.

This procedure was repeated on the diethyl acetal **85** which would give *in situ* generation of the aldehyde under the acidic conditions. Addition of methanol again gave no precipitate and a crude ^1H nmr spectrum of the residue after removal of the solvent was similar to that obtained in the first case. Attempts to precipitate the bisulfite adduct were tedious but ultimately successful when a solid (6 mg, 25% from **85**) was collected after addition of methanol to the crude mixture in water at 0°C.

High field (600 MHz) ^1H nmr illustrated detailed coupling patterns and NOESY and decoupling experiments gave conformational information which is summarised in

Figure 38. It must be stressed that only one diastereomer of the bisulfite adduct **87** was formed in the reaction and is confirmed to be that shown in Figure 38 due to the observed large coupling constant *J* 10.5 Hz between the two protons depicted as H_1 and H_2 - a characteristic value for axial-axial proton interactions. 1D-NOESY experiments performed on the adduct **87** also suggested the molecule to be in the chair conformation shown *i.e.* $^1C_4$ in which the majority of substituents are equatorial as opposed to $^4C_1$.

Figure 38



Further data such as ^{13}C nmr and infra-red spectra were collated and found to correlate well to the literature values for the bisulfite adduct of D-fuconojirimycin.[44] Optical rotation could not be performed due to insufficient material.

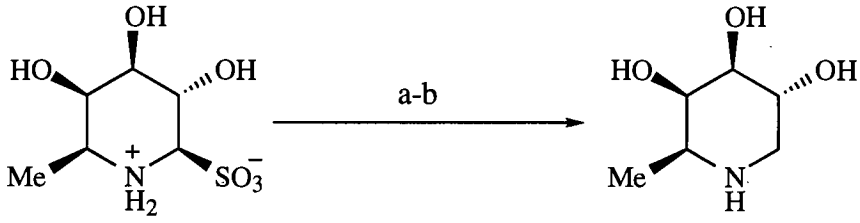
Although a route to a cyclic precursor of deoxyfuconojirimycin had now been established, the yield was low due to isolation problems. After several further attempts using the crude aldehyde **84** as substrate, optimum conditions were achieved resulting in precipitation of the bisulfite adduct after 2 days at 40°C. Filtration of the solid followed by treatment of the mother liquors with methanol and sulfur dioxide resulting in a second batch of solid, gave the bisulfite adduct **87** in an overall yield of 66% from the aldehyde **84**. It was concluded that precipitation of the product was highly dependent on the concentration of the aldehyde in water at the beginning of the reaction and also the amount of methanol added to the mother liquors may have been crucial for maximum isolation of product.

An optical rotation was now attempted due to the availability of sufficient material but to no avail due to a possible contaminant which would not allow the machine to register a value. This was unexpected due to the observed purity in the nmr spectra, but CHN analysis of the same material also failed to give results within the excepted limits.

Deoxyfuconojirimycin

It is well documented that hydrolysis of bisulfite adducts using Dowex ion-exchange resin produce the corresponding azasugars with an anomeric hydroxyl group, whereas saponification with barium hydroxide followed by hydrogenation (H_2, Pd-C, H_2O) yields the deoxy-azasugars. Application of this latter procedure[59] to the bisulfite adduct **87** (Scheme 31) gave a product in 86% yield after cation exchange resin. ^1H and ^{13}C nmr spectra were exceptionally clear and exhibited sharp coupling patterns which correlated well with literature values.[26]

Scheme 31



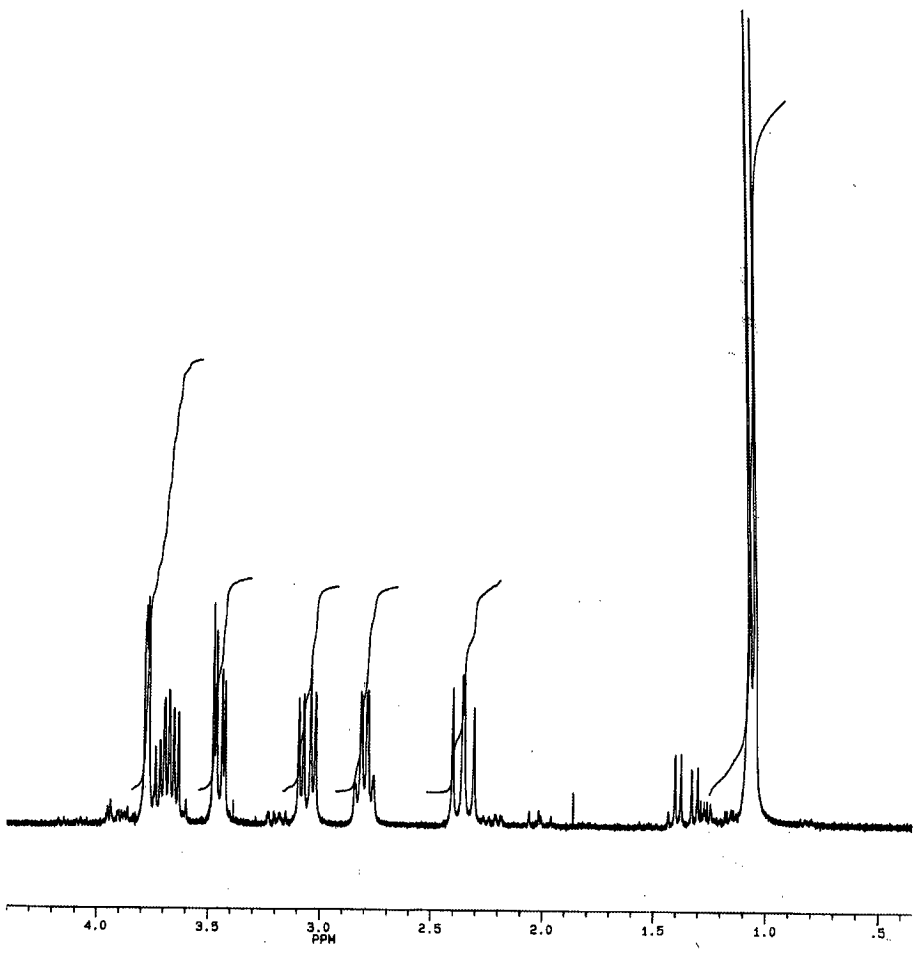
87 **7**

Reagents and conditions: (a) $Ba(OH)_2.8H_2O$, H_2O. (b) Pd-C, H_2, H_2O, 86% (2 steps).

The 250 MHz ^1H nmr spectrum of the product L-deoxyfuconojirimycin **7** is shown in Figure 39. The spectrum highlights the sharp coupling patterns characteristic of the azasugar but also indicates the presence of an impurity with a small coupling pattern in the region δ1.3-1.5, and an attempt to separate this impurity from the product by performing a second purification step through the ion exchange resin failed.

Despite this impurity, unequivocal assignment of this isolated product as L-deoxyfuconojirimycin **7** was obtained by polarimetry whereby the recorded optical rotation was consistent with the literature value, $[\alpha]_D^{21}$ -48.3 (c 0.46, H_2O), lit. $[\alpha]_D^{20}$ -48.8 (c 0.64, H_2O).[26]

Figure 39

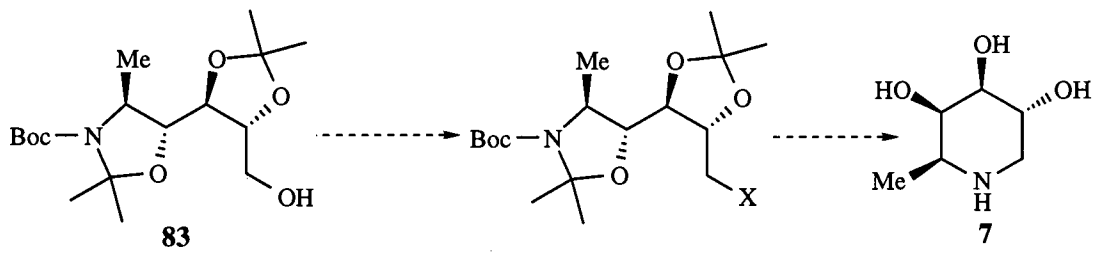


Formation of DFJ provided conclusive evidence that the tentative assignment of stereochemistry during the synthetic pathway was accurate, and also confirmed that no epimerisation of the α-methyl group had occurred under any of the conditions utilised in the synthesis.

3.2.5.3 Alternative ring closure *via* an S_N2 displacement

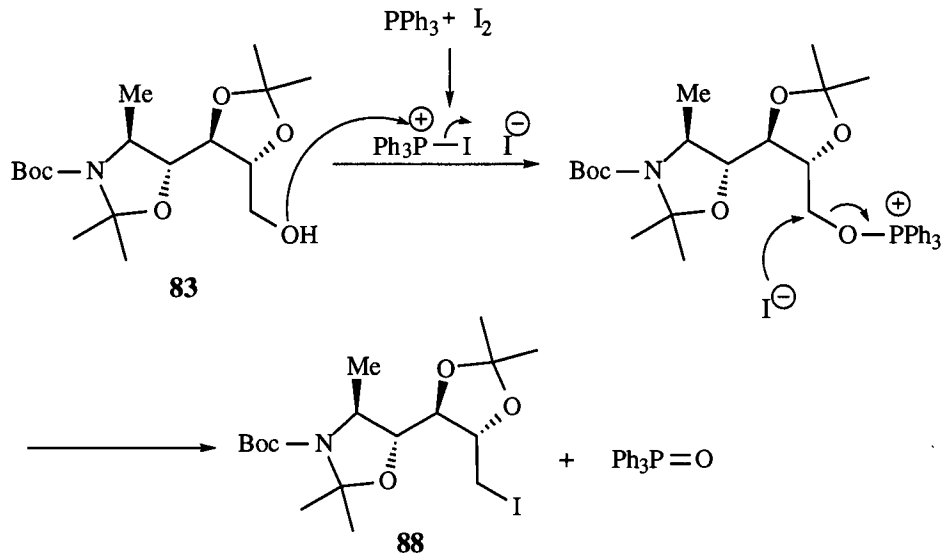
A simultaneous ring closing sequence that was implemented alongside the above route involved the replacement of the primary alcohol in **83** with a halogen in order to align the system for an S_N2 displacement to effect cyclisation as illustrated in Scheme 32.

Scheme 32



This was effected by formation of the alkyl iodide **88** by treatment of the alcohol **83** with triphenylphosphine, iodine, and imidazole in ether/acetonitrile.[98] The mechanism of this process is shown in Figure 40.

Figure 40



The iodo compound **88** was isolated in 45% yield along with recovered starting material on the first and only attempt at this reaction. Addition of this electron withdrawing group into the molecule was evident in the ^{1}H nmr spectrum where a dramatic separation of the low field proton signals now illustrated an ABX system of the CH_2 signal, and sharp coupling patterns of the methine protons. The ^{13}C nmr spectrum also confirmed product formation due to a characteristic high field methylene signal at δ 7.8.

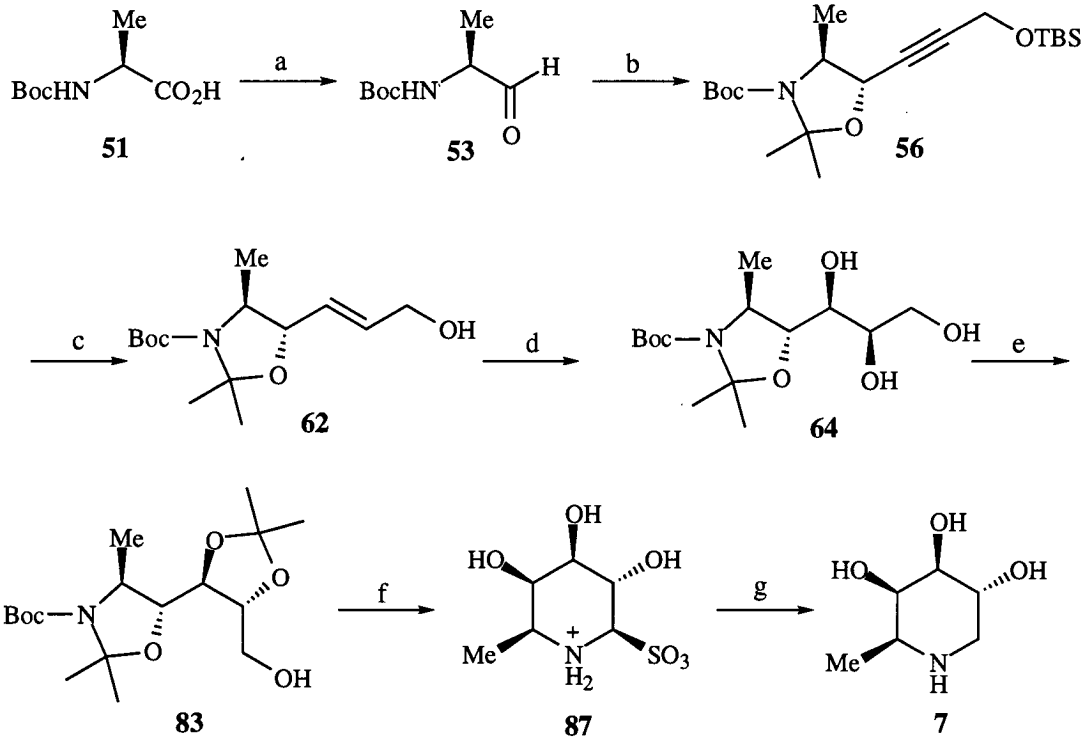
An attempt to convert this iodo-compound **88** to DFJ **7** by removal of the protecting groups was implemented by treatment with aqueous trifluoroacetic acid at room temperature. Analysis by tlc after 4 hours indicated starting material, but after 24 hours only baseline material was observed. The trifluoroacetic acid was removed under

reduced pressure and the crude mixture subjected to ^1H nmr spectroscopy. The resulting spectrum showed no evidence of a cyclised product and very little information was available from the spectrum to assess the actual outcome of the reaction. No other data was collected due to the small scale on which the reaction was performed and due to the sucessful formation of DFJ **7** by the approach *via* the bisulfite adduct **88**.

3.3 SUMMARY OF THE SYNTHESIS OF DFJ

A synthesis of L-deoxyfuconojirimycin **7** has been completed in 14 steps from the commercially available *N*-Boc-L-alanine **51**. Scheme 33 outlines the pathway that was developed for the synthesis.

Scheme 33



Reagents and conditions: (a) i. MeONHMe.HCl, *N*-methyl piperidine, MeOCOCl, DCM, -42°C→r.t., 78%. ii. $LiAlH_4$, THF, ether, -60°C, 82%. (b) i. **54**, MeMgI, ether, -78°C, 62%. ii. 2,2-DMP, $BF_3.OEt_2$, acetone, 68%. (c) i. TBAF, THF, 90%. ii. $LiAlH_4$, THF, -78°C, 90%. (d) OsO_4, NMO, acetone, H_2O, 84%. (e) i. TBS-triflate, 2,6-lutidine, DCM, -10°C, 75%. ii. 2,2-DMP, $BF_3.OEt_2$, acetone, 85%. iii. TBAF, THF, 80%. (f) i. TEMPO, NaOCl,

DCM, 0°C. ii. SO_2, H_2O, 40°C, 66% (2 steps). (g) i. $Ba(OH)_2.8H_2O$, H_2O. ii. H_2, Pd-C, H_2O, 86% (2 steps).

Inhibitory activity of bisulfite adducts of nojirimycin and mannojirimycin and the corresponding deoxyazasugars have been determined against several glycosidases although they possess different activities with respect to their parent deoxyazasugar.[59] Thus, both the bisulfite adduct **87** and DFJ **7** were synthesised in sufficient quantities to be assayed for inhibition of an α(1,3)-FucT-VII by Genzyme Ltd., to observe any similar activity pattern. Unfortunately, at a concentration of 200 μM no inhibition of the enzyme was observed by either substrate suggesting an IC_{50} value well out of useful potency range and no further studies were performed.

3.4 Synthesis Of Deoxyfuconojirimycin Analogues

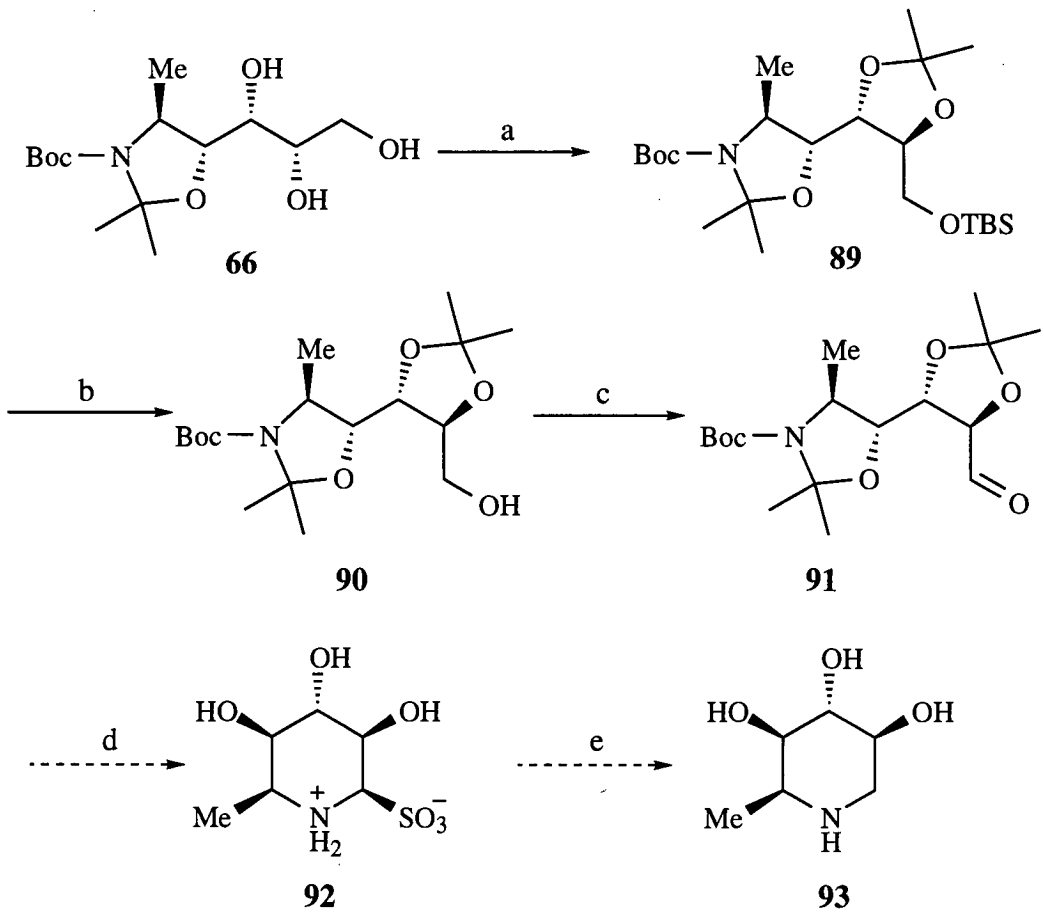
An initial proposal in the design of a synthetic pathway to DFJ was the potential extension and manipulation of the route for the preparation of a range of analogues. Outlined below is a synthesis that was undertaken using a minor diastereomer from the DFJ synthesis, and also some proposed manipulations that could be effective in producing a wide range of synthetic azasugars.

3.4.1 Attempted synthesis of a DFJ azasugar analogue

The synthesis of an azasugar analogue of DFJ was attempted by extension of the minor triol diastereomer **66** resulting from the osmylation of the *E*-alkene **62** (Scheme 23). The synthetic pathway paralleled that used in the route to DFJ and exhibited promising results in the early stages as illustrated in Scheme 34.

The triol **66** was converted to the protected primary alcohol **90** under similar conditions as in the previous synthesis, and oxidation to the aldehyde **91** proved successful. Treatment of the aldehyde **91** with sulfur dioxide gas in water for 2 days failed to result in a precipitate, and addition of methanol also had no effect. Removal of the solvent gave a residue which exhibited a complex ^1H nmr with no evidence of the bisulfite adduct **92**. Several attempts to precipitate the product failed hence the residue was subjected to saponification with barium hydroxide followed by catalytic hydrogenation in an attempt to give the azasugar **93**. The ^1H nmr spectrum of the isolated residue again proved complex and no evidence of the azasugar **93** was observed.

Scheme 34



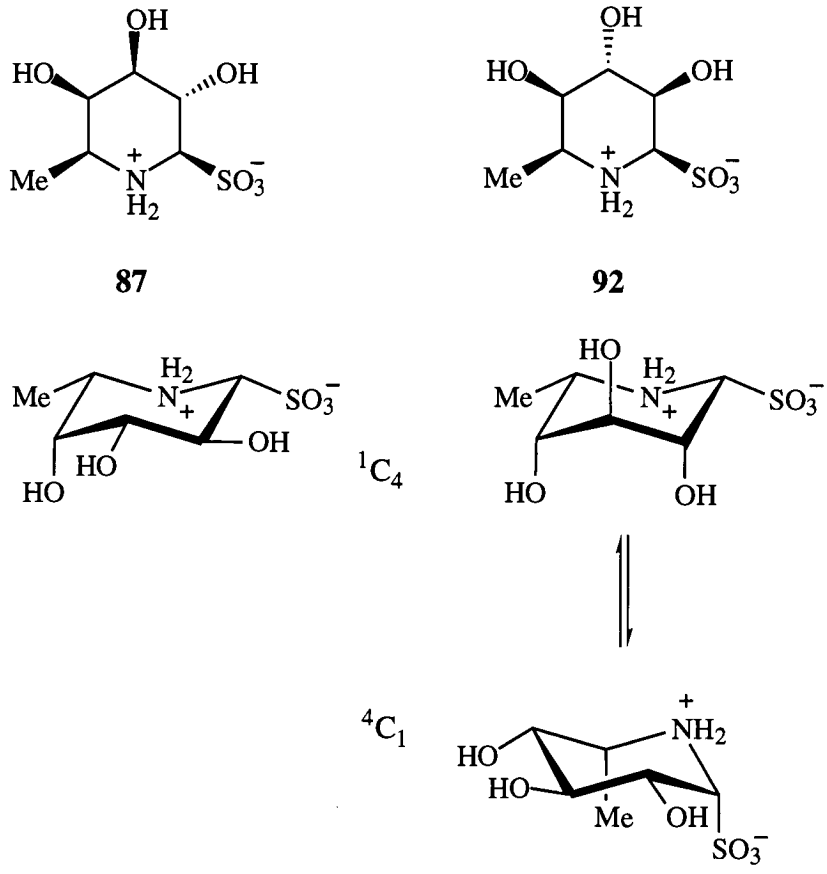
Reagents and conditions: (a) i. TBS-triflate, 2,6-lutidine, -10°C, DCM. ii. 2,2-DMP, $BF_3.OEt_2$, acetone, 62% (2 steps). (b) TBAF, THF, 80%. (c) TEMPO, NaOCl, DCM, 0°C, 83%. (d) SO_2, H_2O, 40°C. (e) i. $Ba(OH)_2.8H_2O$, H_2O, ii. Pd-C, H_2O.

As reported in the previous synthesis of DFJ, precipitation of the bisulfite adduct **87** was crucial for isolation of pure product. Problems in the precipitation of the adduct **92** may be due to two factors; 1) the concentration of the substrate **92** in the solvent was too dilute; and 2) the difference in stereochemistry of this adduct may result in a difference in properties. Taking into consideration this second factor a comparison between the two bisulfite adducts **87** and **92** is depicted in Figure 41.

If the conformation of the bisulfite adduct **92** is depicted in the $^1C_4$ conformation, as in the case for **87** it will contain 3 axial hydroxyl groups which will result in a higher energy conformer than **87**, however if positioned in the $^4C_1$ conformation- the bulky methyl and sulfur groups are then axial and will pose large steric interactions. This

energy barrier and steric interactions may have a significant effect on the properties of the compound **92** resulting in difficulties in isolation.

Figure 41



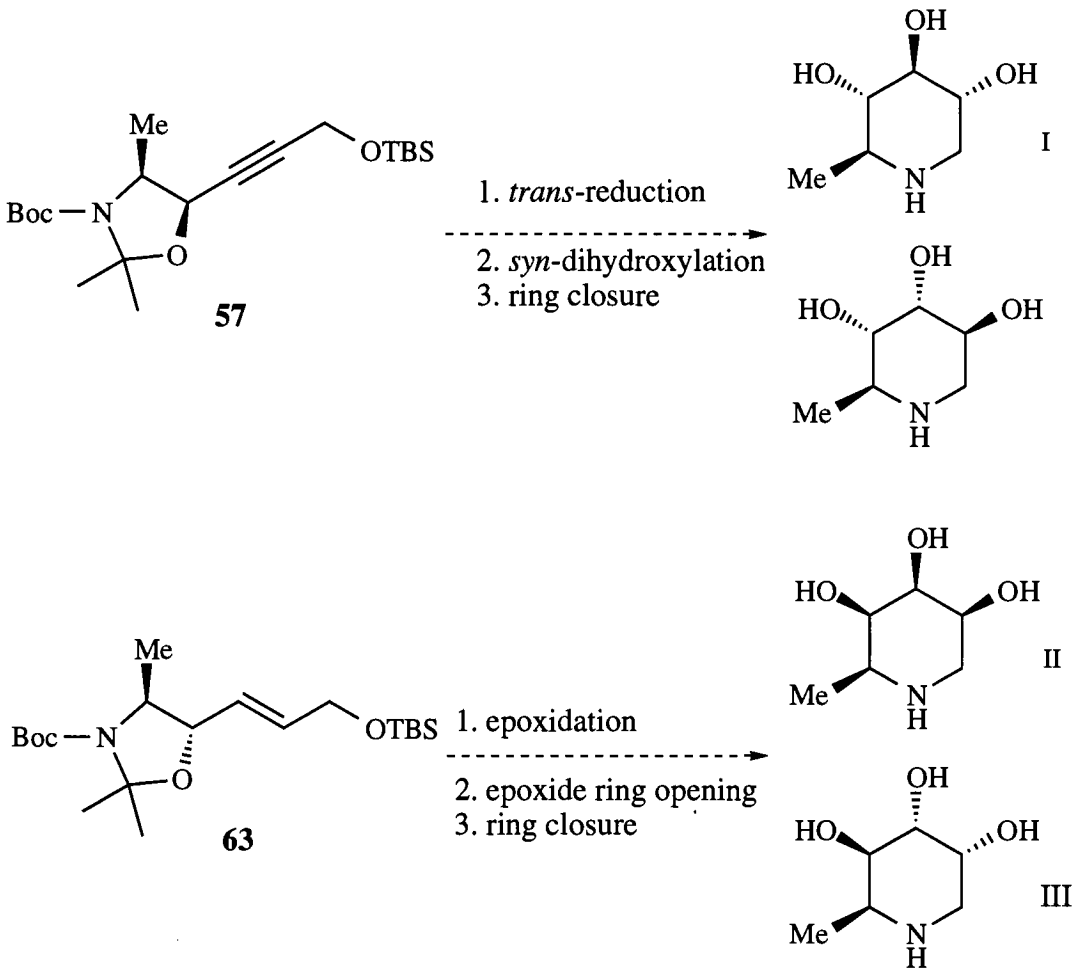
This synthesis of the azasugar **93** was not repeated due to time constraints and the lack of the diastereomer **66** due to the significant decomposition of this triol diastereomer.

3.4.2 Potential manipulations for analogue generation

Although time did not permit the manipulation and extended syntheses of other L-deoxyazasugar analogues, Figure 42 illustrates some possible transformations that could be performed from intermediates or minor diastereomers from the above methodology. Some of the azasugars shown overleaf have been previously synthesised by Streith and Defoin[43] in both the racemic form and asymmetrically to give the D-azasugars *via* the corresponding bisulfite adducts ultilising the hetero-Diels Alder approach.

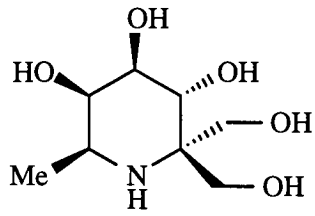
Additionally, by utilising the D-alanine amino acid precursor *N*-Boc-D-alaninal, an asymmetric synthesis of a range of D-azasugars could be performed *via* a similar synthetic pathway to that developed.

Figure 42



I: 1,5-imino-1,5,6-trideoxyglucitol, (glucose derivative); II: (talose derivative); III: (gulose derivative)

4. Synthesis Of 1,1-*Bis*-Hydroxymethyl-1,5-Dideoxy-1,5-Imino-L-Fucitol



27

4.1 Extension Of The Route Used In The Synthesis Of DFJ

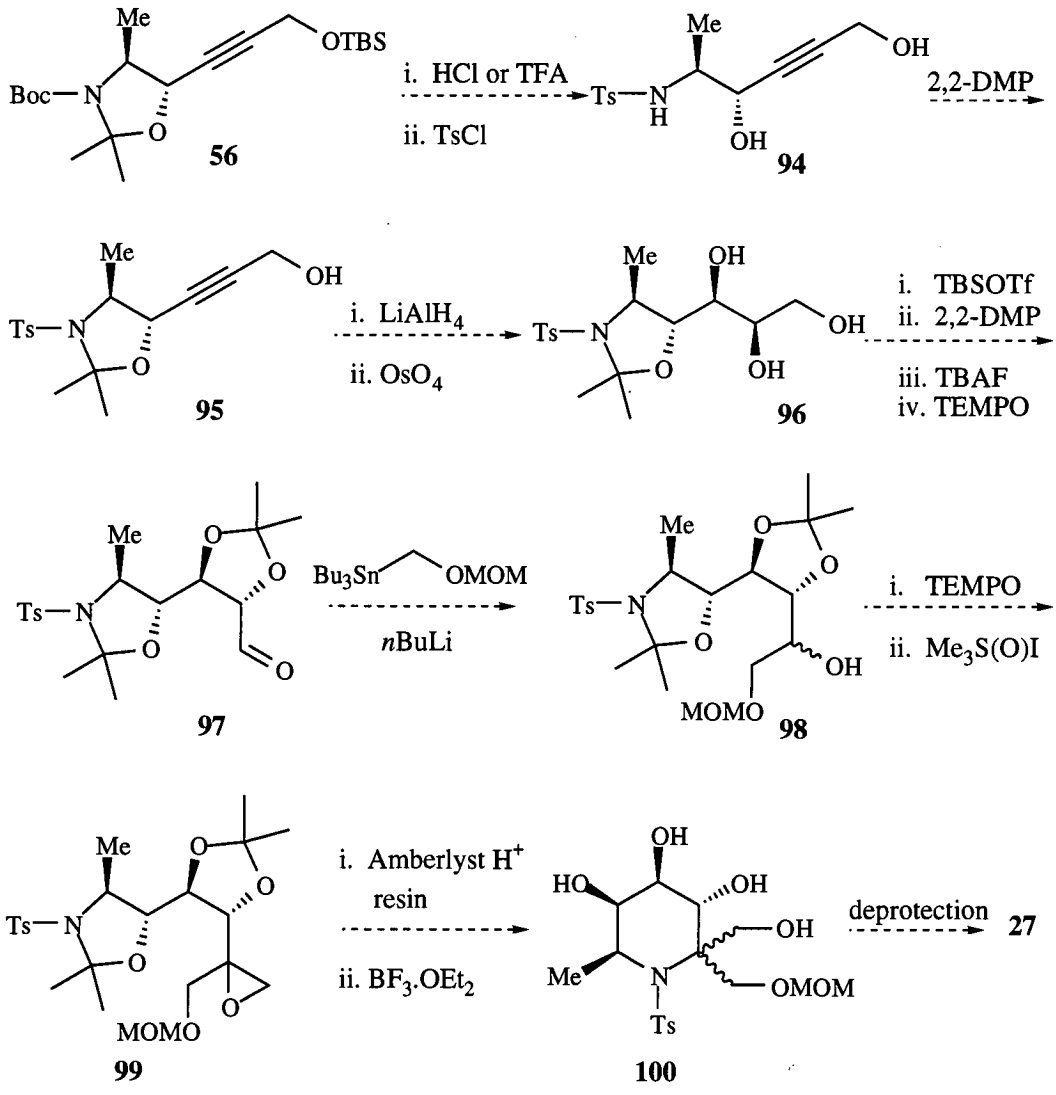
4.1.1 Proposed route

The aim of the project after the deoxyfuconojirimycin synthesis was to extend and elaborate the synthetic pathway to allow further functionalisation to yield the key target molecule 1,1-*bis*-hydroxymethyl-1,5-dideoxy-1,5-imino-L-fucitol, **27**.

A proposed route to the polyhydroxylated piperidine **27** utilising some of the methodology from the synthesis of DFJ is outlined in Scheme 35 and illustrates the extension of the synthesis from the oxazolidine **56**.

The initial synthetic challenge involved removal of the *N*-Boc protecting group in the oxazolidine **56** and *N*-sulfonation to give the *N*-Tosyl amide **94**. The *N*-Tosyl protecting group is necessary for a 6-*exo-tet* cyclisation to be implemented later in the pathway for piperidine ring formation as described in section 2.1. It was anticipated that introduction of the hydroxyl groups could be achieved by initial formation of the *E*-alkene followed by a *syn*-dihydroxylation to give the triol **96** using conditions optimised in the previous synthesis. The first of the two hydroxymethyl groups was anticipated to be introduced by treatment of aldehyde **97** with [(methoxymethyl) methyl]lithium generated *in situ* from [(methoxymethyl)methyl]tributylstannane and *n*-butyllithium.[99-101] The second hydroxymethyl group would be generated after cyclisation of the tosylated nitrogen group onto the epoxide **99** to give the polyhydroxylated piperidine **100**.

Scheme 35

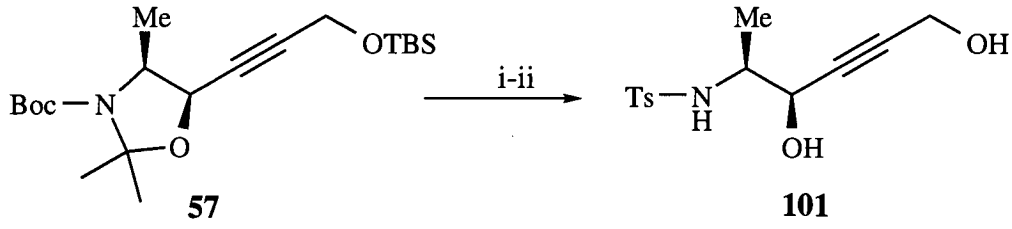


4.1.2 Nitrogen protecting group manipulation

Removal of the *N*-Boc protecting group was required to enable reprotection of the nitrogen with the tosyl group. Standard acidic deprotection conditions of 3M hydrochloric acid in EtOAc or trifluoroacetic acid were implemented on the minor oxazolidine diastereomer **57** to achieve optimum conditions and to avoid unnecessary depletion of stocks of the major diastereomer **56**, (Scheme 36). Attempts using 3M hydrochloric acid in EtOAc and subjecting the crude residue to tosyl chloride with catalytic DMAP in pyridine failed to give any product due to the low solubility of the residue in the solvent. Repetition of the reaction using different tosylation conditions

(TsCl, Et_3N, DCM) did give a white solid as product albeit in moderate yield (56%). Nmr spectroscopy of the isolated product was performed in deuterated DMSO and the ^1H nmr spectrum illustrated sharp coupling patterns with characteristic coupling constants which correlated well for the β-amino alcohol **101**.

Scheme 36



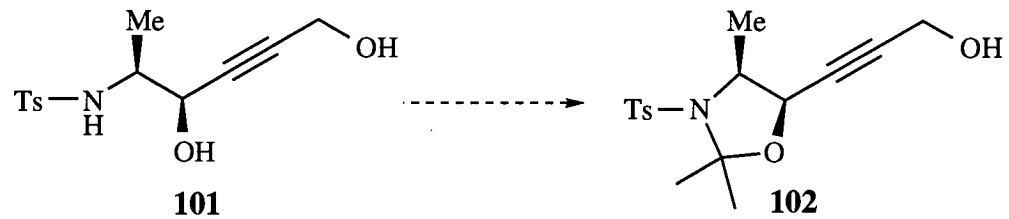
57 **101**

Reagents and conditions: i. 3M HCl, EtOAc, ii. TsCl, Et_3N, DCM (56% 2 steps); or i. TFA, 0°C. ii. TsCl, Et_3N, DCM, 1,4-dioxane, (51% 2 steps).

An attempt to cleave the Boc group using trifluoroacetic acid followed by tosylation (TsCl, Et_3N, DCM) gave **101** but in low yield (25%), until it was noted that addition of 4 equivalents of triethylamine in the second step improved the yield of product to 44%. Use of 1,4-dioxane as co-solvent in a repeat of tosylation conditions improved the yield of isolated product to 51% with only 2 equivalents of triethylamine due to increased solubility of the substrate in the mixed solvent.

Two attempts to form the corresponding oxazolidine **102** by treatment of **101** with 2,2-dimethoxypropane and boron trifluoride etherate in acetone (Scheme 37) only resulted in multispot mixtures when monitored by tlc and no product was isolated.

Scheme 37



101 **102**

Reagents and conditions: 2,2-DMP, $BF_3.OEt_2$, acetone.

Conclusion

As a result of obtaining the tosylated product **101** in low-moderate yields and difficult formation of the corresponding oxazolidine **102**, this route to the polyhydroxylated

piperidine **27** was abandoned without application of the methodology to the major diastereomer **56**. The low yield of tosylated product could be due to the polar nature of the resulting amine which under the conditions used also cleaves the silyl protecting group to reveal the free hydroxyl group. Continuation of the synthesis at this stage seemed impractical when considering the number of steps ahead.

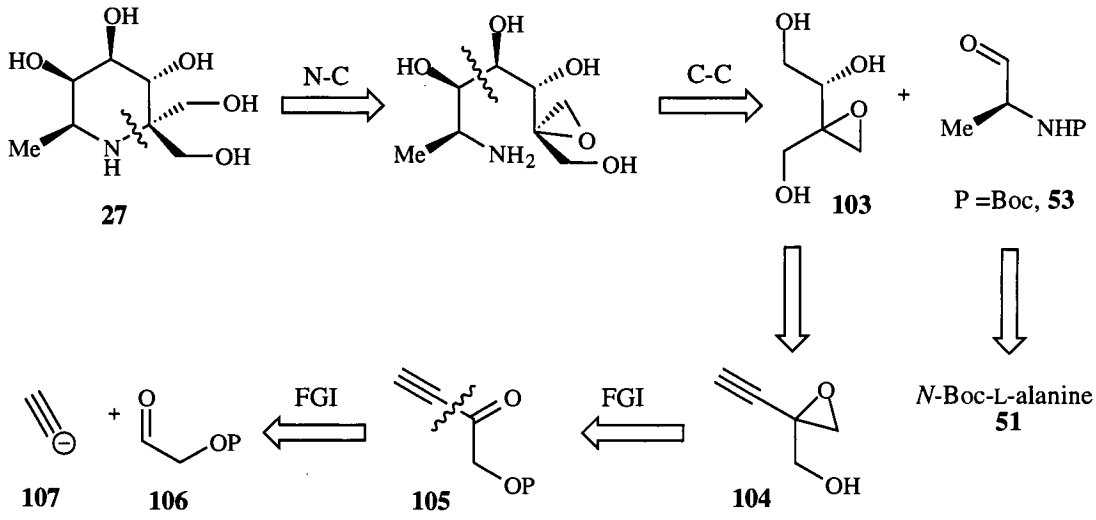
Thus, a novel route to the target molecule **27** was developed to enable a more convergent synthesis to be performed whilst incorporating some of the methodology so far developed.

4.2 Revised Route To 1,1-*Bis*-Hydroxymethyl-1,5-Dideoxy-1,5-Imino-L-Fucitol

4.2.1 Proposed route

A retrosynthetic analysis of the target molecule **27** is outlined in Scheme 38 and highlights the key disconnections and functional group interconversions that could be performed using some of the developed methodology.

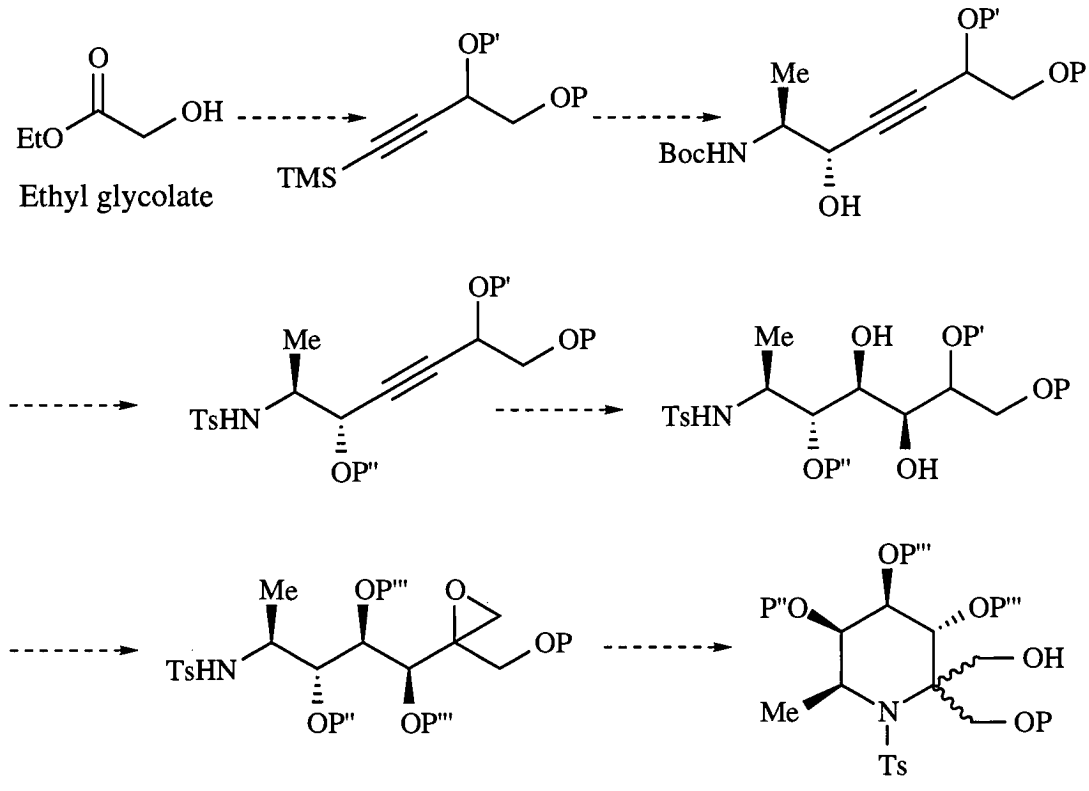
Scheme 38



Disconnection of the N-C and C-C bonds reveals two fragments - the α-amino aldehyde **53** which is available from *N*-Boc-L-alanine **51**, and a polyhydroxylated fragment **103**. Functional group interconversions of **103** yields the epoxy-acetylene **104** which in turn can be derived from the α,β-acetylenic ketone **105**. A further disconnection of **105** gives two synthons **106** and **107** as shown.

A synthetic pathway proposed from this retrosynthetic analysis is descibed in Scheme 39 and involves the construction of the acetylene unit containing one of the hydroxymethyl substituents required, before addition to *N*-Boc-L-alaninal **53**. Although a protecting group strategy is required to enable orthogonal deprotection, further functionalisation will then be possible utilising methodology from the synthesis of DFJ. This pathway fulfils the aim of the project by retaining the flexibility to allow preparation of analogues *en route* to the target molecule **27** by minor manipulations of the synthetic route.

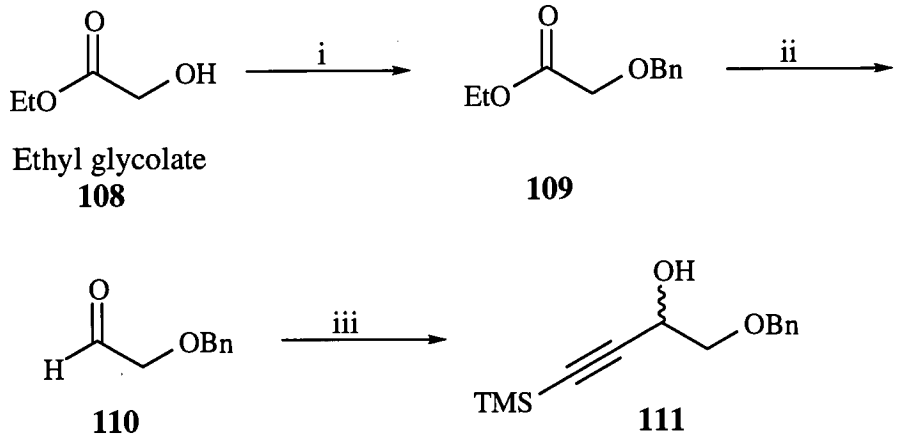
Scheme 39



4.2.2 Synthesis of the acetylene unit

The readily available and inexpensive precursor for the assembly of the acetylene unit is ethyl glycolate **108**. Protection of the free hydroxyl group in ethyl glycolate as the benzyl ether **109** was effected by treatment with benzyl bromide and silver (I) oxide in refluxing ether[102] (Scheme 40). Attempts using benzyl bromide under various other conditions such as sodium hydride/tetrabutylammonium iodide/THF, sodium hydride/DMF, potassium carbonate/acetone gave little or no desired product.

Scheme 40



Ethyl glycolate
108

109

110

111

Reagents and conditions: i. BnBr, Ag_2O, ether, reflux, 82%. ii. DIBAL (1M in toluene), DCM, -78°C, 60%. iii. *Bis*-trimethylsilyl acetylene, MeLi:LiBr, THF, 0°C, 75%.

Reduction of the ester **109** to the aldehyde **110** was then attempted using di-*iso*butylaluminium hydride (1M solution in toluene) in DCM.[103] On small scale (<1g) the aldehyde was isolated after column chromatography in excellent yields of 80-90% with no evidence of any over reduction to the corresponding alcohol. Scale up of the reaction led to problematic work ups due to formation of a thick emulsion which required tedious separations and resulted in slightly reduced yields. Use of di-*iso*butylaluminium hydride as a molar solution in DCM on small scale proceeded well however a significant impurity was present when visualised by tlc and was difficult to separate from the product resulting in contamination of the aldehyde **110**.

Introduction of the silylacetylene unit to the aldehyde **110** was effected by initial displacement of a single trimethylsilyl group from *bis*-trimethylsilylacetylene using methyllithium in THF according to the procedure of Holmes *et al.*[104] Addition of 1.6-1.8 equivalents of the mono-lithiated TMS-acetylene to the aldehyde **110** resulted in the racemic propargyl alcohol[105] **111** in good yields (70-80%). Use of 1.2-1.5 equivalents of the lithiated acetylene resulted in lower yields (11-57%) of the propargyl alcohol **111**.

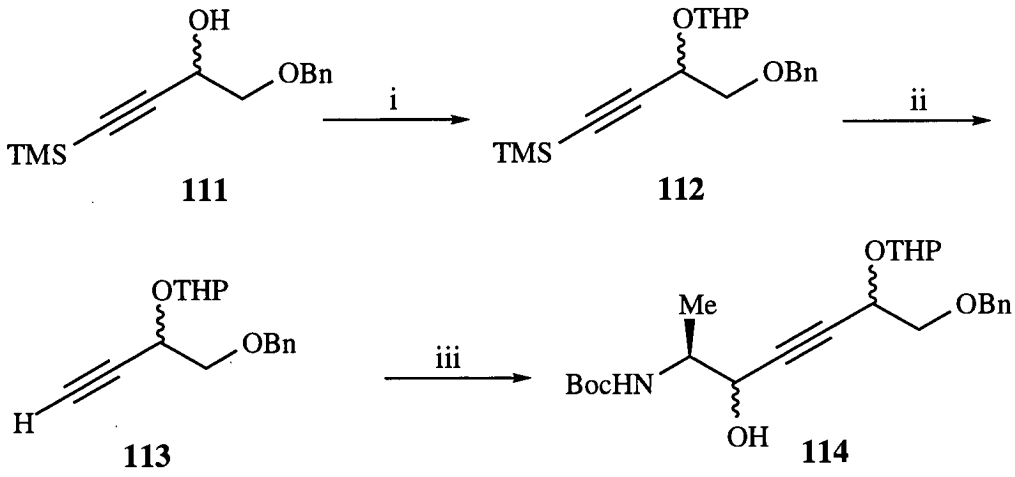
Hydroxyl protection

Protection of the hydroxyl function in **111** was required before attachment of the acetylene unit to *N*-Boc-L-alaninal **53** to avoid any potential side reactions occurring at

the hydroxyl group. The tetrahydropyranyl ether (THP) was chosen as protecting group due to its stability towards basic reaction conditions and organometallic reagents yet potential cleavage under mild acidic conditions which prove ideal for the proposed pathway. The THP ether **112** was formed by treatment of the propargyl alcohol **111** with 3,4-dihydro-2*H*-pyran and *para*-toluenesulfonic acid in DCM[106] in 84% yield. The ^{1}H nmr spectrum was complex due to the resultant diastereomers but in conjunction with the ^{13}C nmr spectrum it was evident that the THP ether had formed.

Treatment of the THP ether **112** with methanolic potassium carbonate[105] cleaved the trimethylsilyl group to give the terminal acetylene **113** in 90% yield.

Scheme 41



Reagents and conditions: i. 3,4 dihydro-2*H*-pyran, *p*TSA, DCM, 84%. ii. K_2CO_3, MeOH, 90%. iii. *N*-Boc-L-alaninal **53**, *n*BuLi, THF, -100°C, 56%.

Two equivalents of the terminal acetylene **113** were then treated with *n*-butyllithium in THF at low temperature to form the corresponding lithium acetylide, and *N*-Boc-L-alaninal **53** added dropwise in THF. After several minutes the reaction was quenched and extracted at room temperature to yield, after chromatography, the recovered terminal acetylene **113** and β-amino alcohol **114** (56%). Unfortunately, due to the presence of 4 stereogenic centres in the isolated product **114** the ^{1}H and ^{13}C nmr spectra were complex and although the product was verified as that expected, the ratio of the diastereomers formed in this step could not be deduced due to the complexity of the spectra.

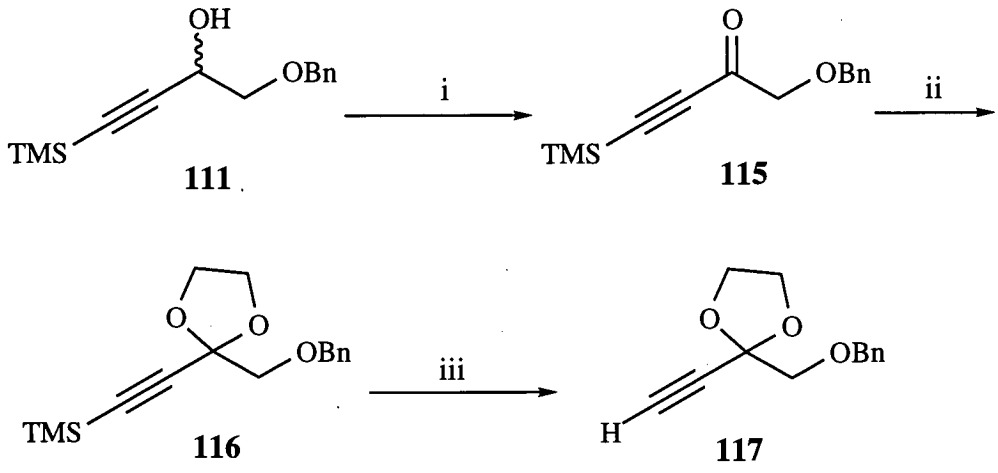
This route showed promise in that the two units, the acetylene **113** and the α-amino aldehyde **53** could be combined by the acetylide addition, however the poor choice of

hydroxyl protecting group was evident and the resulting products **114** could not be characterised fully by nmr due to the high number of stereocentres. As a result of this it was anticipated that a different protecting group strategy which would simplify the spectra would allow the synthesis to continue.

Carbonyl protection

The stereocentre in the racemic propargyl alcohol **111** was removed by oxidation to the α,β-acetylenic ketone **115** utilising the TEMPO-mediated oxidative procedure,[90] (Scheme 42). Protection of the ketone as the 1,3-dioxolane was chosen due to its stability under basic conditions and cleavability under acidic conditions which were again ideal for the proposed synthetic route. The ketal **116** was obtained in favourable yields after treatment of the α,β-acetylenic ketone **115** with ethylene glycol and trimethylsilyl chloride in DCM.[107]

Scheme 42



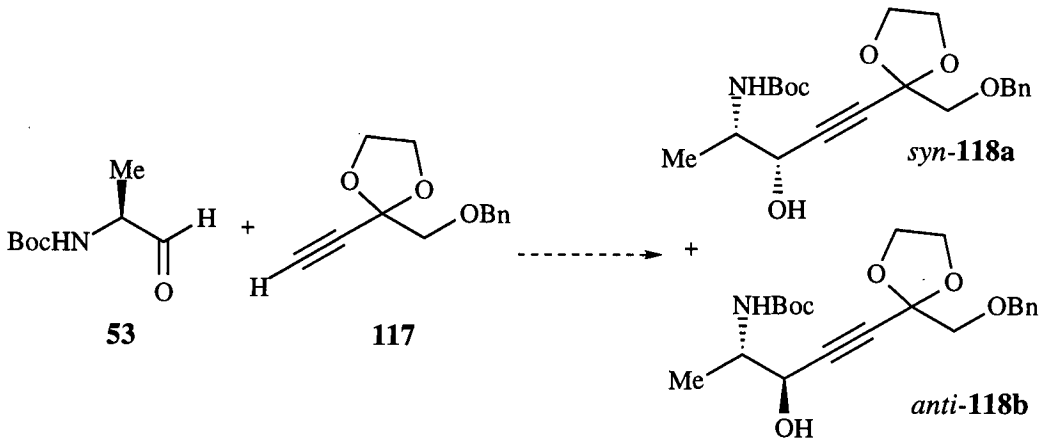
Reagents and conditions: i. TEMPO, NaOCl, BTAC, NaBr, sat. aq. $NaHCO_3$, sat. aq. NaCl, DCM, 0°C, 97%. ii. $HOCH_2CH_2OH$, TMSCl, DCM, 88%. iii. K_2CO_3, MeOH, 93%.

Removal of the trimethylsilyl group of **116** in methanolic potassium carbonate gave the terminal acetylene **117** in excellent yields, use of tetrabutylammonium fluoride in THF also gave the acetylene **117** albeit in lower yields.

4.2.3 Acetylide addition to *N*-Boc-L-alaninal

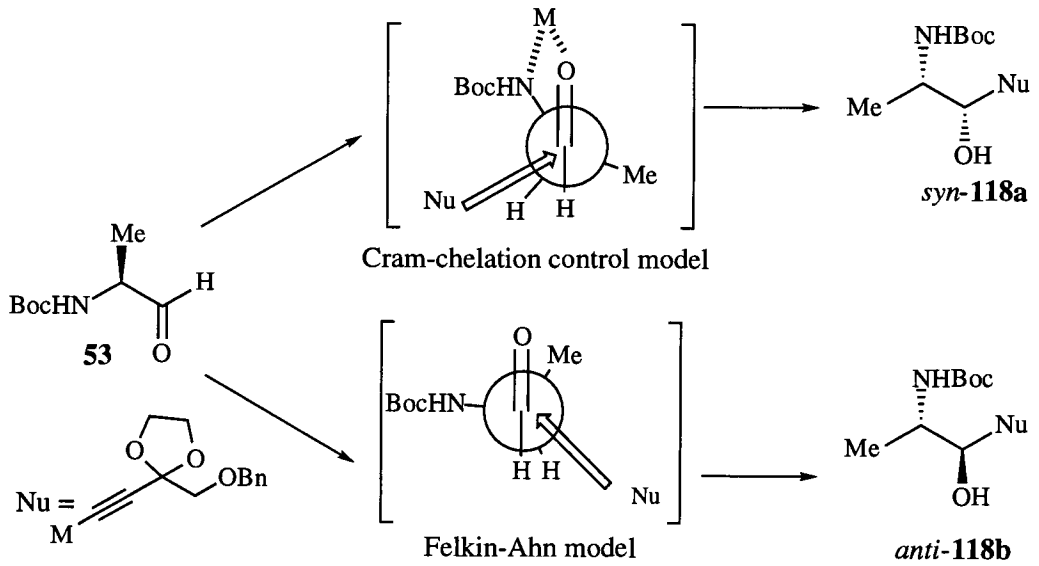
Addition of the achiral acetylene **117** to the prochiral α-amino aldehyde **53** was investigated more thoroughly than the similar reaction performed in the DFJ synthesis (Chapter 3, Scheme 19). It was anticipated that by utilising different metals and solvent systems the ratio of the resulting β-amino alcohols **118a/b** could be improved in favour of the desired diastereomer **118a** which contains the required stereochemistry of the newly formed stereogenic centre, (Scheme 43).

Scheme 43



The β-amino alcohol **118a** is expected to result from Cram-chelation control in the transition state (Figure 43), whereas non-chelation control is anticipated to proceed *via* the Felkin-Ahn model where the most stable conformation of the transition state is proposed to be that where the largest group is orthogonal to the plane of the carbonyl group, resulting in the *anti*-isomer **118b**.

Figure 43



Due to the presence of the nitrogen group in **53** it was anticipated that chelation control would be possible hence favouring the formation of the *syn*-adduct **118a**.

Literature precedence for the addition of acetylenes to aldehydes has highlighted that several factors can influence the diastereoselectivity of such reactions, *e.g.* solvent, counter-ion, the nature of the ligating group, and also the nature of the nucleophile.[108-111] Consequently, a series of reactions were performed using different addition methods according to literature procedures to effect formation of the β-amino alcohols **118a/b** and these are outlined below;

Method 1, Addition of the lithium acetylide in THF[112]

i. **117**, *n*BuLi, THF, -78°C. ii. *N*-Boc-L-alaninal **53**, THF.

Method 2, Addition of the lithium acetylide in ether

as method 1, in ether.

Method 3, Addition of the Grignard acetylide formed *via* transmetallation[113]

i. **117**, *n*BuLi, THF, -78°C. ii. $MgBr_2$. iii. *N*-Boc-L-alaninal **53**, THF.

Method 4, Addition of the Grignard acetylide in THF at room temperature[114]

i. **117**, EtMgBr, THF, 0°C→r.t. ii. *N*-Boc-L-alaninal **53**, THF, r.t.

Method 5, Addition of the Grignard acetylide in THF at low temperature

i. **117**, EtMgBr, THF, 0°C→r.t. ii. *N*-Boc-L-alaninal **53**, THF, -78°C.

Method 6, Addition of the Grignard acetylide in THF at low temperature- different addition[71,109]

i. **117**, EtMgBr, THF, 0°C→r.t. ii. *N*-Boc-L-alaninal **53**, THF, -78°C.

Method 7, Addition of the copper acetylide[108,115]

i. **117**, EtMgBr, THF, 0°C→r.t. ii. CuI, Me_2S, THF, -78°C. iii. *N*-Boc-L-alaninal **53**, THF, -30°C.

Method 8, Addition of the zinc acetylide[108,110]

i. **117**, *n*BuLi, THF, -78°C. ii. $ZnBr_2$. iii. *N*-Boc-L-alaninal **53**, THF, -78°C.

The results obtained are shown in Table 1.

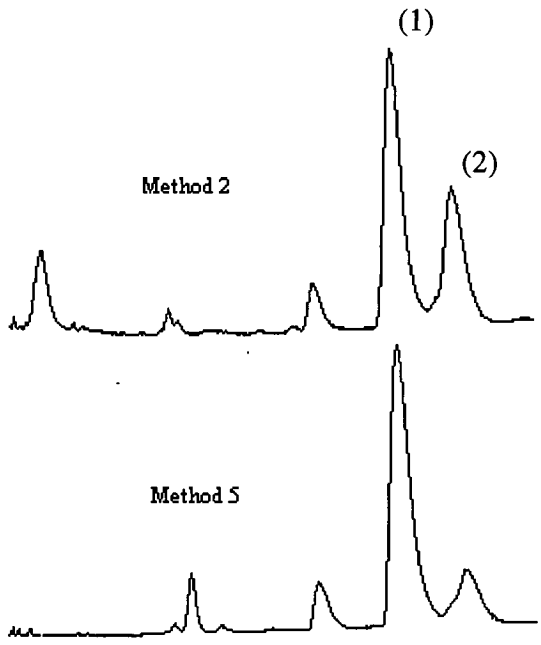
Table 1

Method[a]	Metal	Solvent	Temp[b]	Yield[c] (%)	118a:118b[d]
1	Li	THF	-78°C	55	78:22
2	Li	ether	-78°C	44	70:30
3	MgBr	THF	-78°C	56	**90:10**
4	MgBr	THF	rt	69	71:29
5	MgBr	THF	-78°C	59	**90:10**
6	MgBr	THF	-78°C	77	86:14
7	CuI	THF	-78°C	44	74:26
8	ZnBr	THF	-78°C	18	-

[a] 2.2 equivalents of the acetylene **117** was used in each case. [b] The temperature stated is that on addition of the acetylene and *N*-Boc-L-alaninal. [c] The combined yield of β-amino alcohols **118a** and **118b** isolated after column chromatography of the crude mixture, is given as a percentage of the amount of *N*-Boc-L-alaninal **53** used in the reaction. [d] The ratio of diastereomers was determined by HPLC using a Baker Chiralcel OD (4.6 x 250) column and detected by a Waters 486 tunable absorbance detector (λ 254 nm). The column was eluted with 95:5 hexane/IPA at a flow rate of 0.2 ml/min.

The ratio of diastereomers was deduced by HPLC analysis of the combined diastereomer mixture obtained after column chromatography of the crude mixture to remove unreacted starting material and other impurities. A representative sample of the HPLC chromatograms obtained is shown in Figure 44 and highlights that even after chromatography some impurity is still present. The ratio of the two isomers was determined by the area difference of the corresponding peaks and two examples are given for comparison in Figure 44 and correspond to the lowest and highest ratio of diastereomers obtained resulting from method 2 and 5 respectively.

Figure 44



R_T = Peak 1, 67 minutes
Peak 2, 79 minutes

In the methods 1-7 utilised for the β-amino alcohol **118** formation it was evident from the HPLC chromatograms that the same diastereomer dominated, i.e. no interchange of the corresponding peaks 1 and 2 in the chromatograms was observed. Consequently, it was proposed that the major diastereomer was that resulting from Cram-chelation control in the transition state hence yielding the desired β-amino alcohol **118a**. The configuration of the major diastereomer was confirmed as that for the β-amino alcohol **118a** as descibed later in section 4.2.4.1.

Table 1 highlights some interesting aspects. Initially, the lithium acetylide addition (method 1) was attempted as a model system as it is known to show low diasteroselectivity when added to chiral α-alkoxy aldehydes.[110] Even so, addition of the α-amino aldehyde **53** to the *in situ* generated lithium acetylide produced a moderate diastereomeric excess (78:22). The influence of solvent in these type of reactions was highlighted by a drop in diastereoselectivity (70:30) when the same reaction was performed in ether (method 2).

An improvement in diastereoselectivity was observed by use of the corresponding Grignard acetylide at low temperature. Different methods using the Grignard acetylide were employed which included different addition modes (method 5 and 6), temperature (method 4), and formation of the *in situ* generated metal acetylide (method

3 and 5). Methods 3 and 5 which were essentially the same although involved slightly different ways of forming of the Grignard reagent, resulted in the best overall diastereoselectivity (90:10) of the resulting β-amino alcohols **118a/b**. Method 6 was a similar procedure to that utilised in the DFJ synthesis (Chapter 3, Scheme 19) and differed from method 5 only in the mode of addition, however a slight decrease in diastereomer ratio was observed. An attempt to repeat method 5 in ether was abandoned due to the insolubility of the forming Grignard reagent in the solvent.

The addition of the copper acetylide was attempted following a report by Herold[108] in which an acetylene unit was added to a *N*-Boc-serine derivative with very high selectivity *via* chelation control in the transition state. Application of this methodology to the acetylene **117** and *N*-Boc-L-alaninal **53** was performed but resulted in a low diastereoselectivity (74:26). The low selectivity was paralleled by experiments reported by Reetz and co-workers[109] who concluded that vinyl and phenyl copper reagents produced lower diastereoselectivity on addition to α-amino aldehydes with respect to alkyl reagents, and although no alkynyl reagents were reported it was anticipated that these would parallel that of the vinyl type reagents.

Method 8 employing the zinc bromide additive proved problematic due to the complexity of the reaction mixture when monitored by tlc. A product corresponding to the amino alcohols **118a/b** was isolated however the ^{1}H nmr of the mixture was complex and contaminated hence the mixture was not subjected to HPLC analysis.

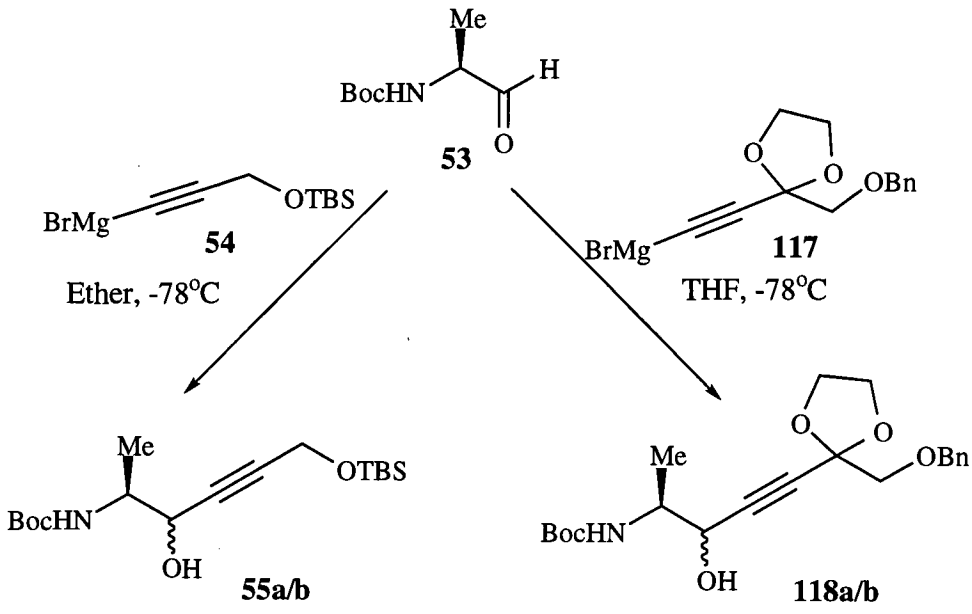
Conclusion

A satisfactory ratio of β-amino alcohols **118a/b** was obtained (90:10) in the procedures of method 3 and 5 and repetitions of the experiment were performed using the procedure in method 5 where *N*-Boc-L-alaninal was added to the Grignard acetylide (formed from ethylmagnesium bromide) in THF at low temperature. Repetitions of the reaction utilising method 3 were inconsistent and difficult to implement due to the insolubility of the magnesium bromide in THF and hence the difficult addition of the slurry to the reaction mixture.

It is evident from both the HPLC and nmr spectra of the resulting β-amino alcohols **118a/b** that little or no epimerisation of the α-methyl group has occurred under the conditions used in methods 1-7, which was also the case reported by Reetz.[109]

This study highlighted several key factors such as the effect of the solvent, temperature, metal and addition modes. An interesting effect that emerged from the experiments was the observed increase in selectivity between the addition of the acetylide of **117** (method 6 above) as compared to that of the acetylide of **54** (Chapter 3, Scheme 19) using the conditions adapted from Hanson and Lindberg.[71] Figure 45 outlines the two reactions.

Figure 45



Ratio (NMR) approx. 2:1

Ratio (HPLC) approx. 6:1

This improvement in selectivity is proposed to result from a combination of effects including the increased size and functionality of the acetylene **117** with respect to that of **54** and the different solvent used, although the improved method of deducing the diastereomeric ratio would also result in a more accurate value.

4.2.4 Continuation of the synthesis:- Hydroxyl and nitrogen protecting group manipulation

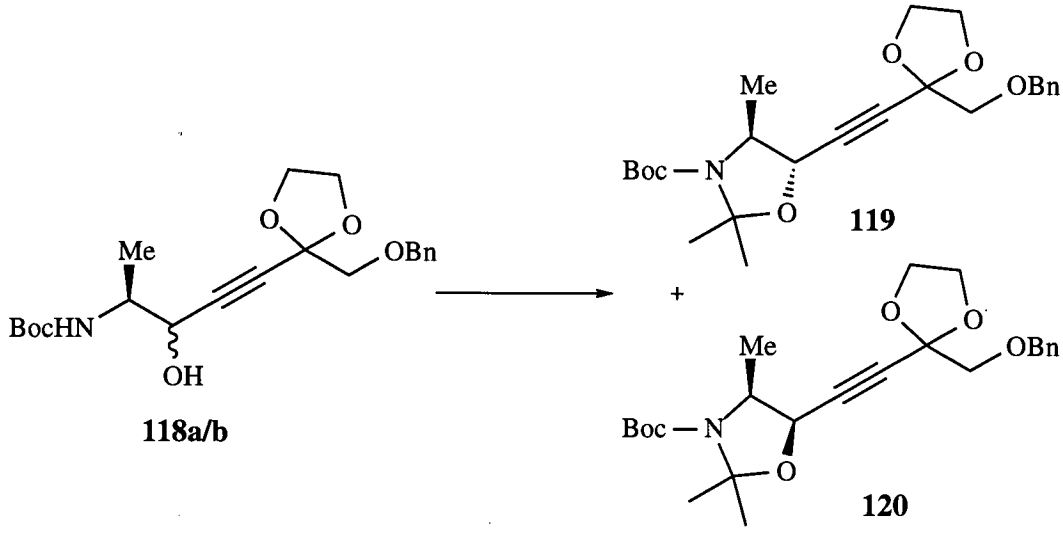
Elaboration of the β-amino alcohols **118a/b** was undertaken and proceeded *via* several different pathways due to unforeseen problems. This section will outline the attempted routes and the outcome.

4.2.4.1 Oxazolidine formation and nitrogen protecting group manipulation

Oxazolidine formation

It was anticipated that oxazolidine formation of the β-amino alcohols **118a/b** would allow separation of the corresponding oxazolidines by column chromatography, hence enabling nmr experiments to be performed to confirm the configuration at the newly formed stereocentre and also to allow continuation of the synthesis on the single diastereomer **119**, (Scheme 44).

Scheme 44



Reagents and conditions: see Table 2.

Treatment of the mixture of β-amino alcohols **118** under the conditions used previously for oxazolidine formation (2,2-DMP/BF_3.OEt_2/acetone) gave only a low yield of oxazolidine products **119/120** with recovered starting material **118a/b**. This result was unexpected due to its previous success hence several other conditions were used and the results are summarised in Table 2.

Nmr spectra of the isolated mixture of diastereomers although complex confirmed oxazolidine formation due to the presence of the two additional methyl signals in both the ^1H and ^{13}C nmr spectrum.

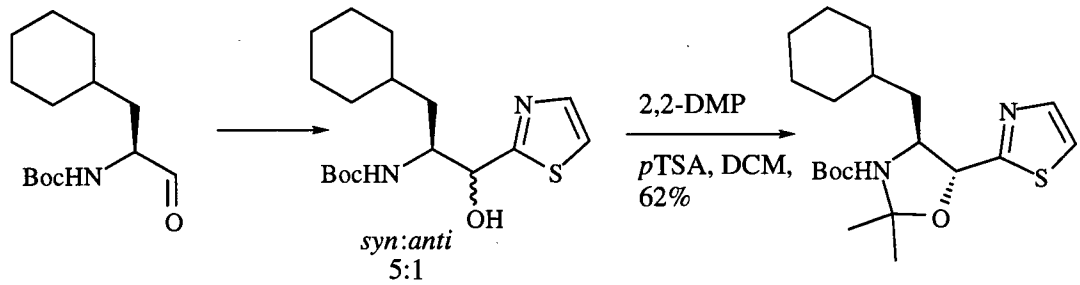
Table 2

Reaction Conditions[a]	**Yield**[b]**, %**
2,2-DMP, $BF_3.OEt_2$, acetone.	26
2,2-DMP, $BF_3.OEt_2$, acetone, 4Å sieves.	57
2,2-DMP, $BF_3.OEt_2$, DCM.	63
2,2-DMP, $BF_3.OEt_2$, DCM, 4Å sieves.	55
2,2-DMP, *p*TSA.	44
2,2-DMP, *p*TSA, DCM, reflux.	80

[a] All reactions were performed using the same quantites of substrate (100mg), 2,2-DMP (1.5ml), catalyst and solvent (2ml) at the temperature stated and were monitored by tlc until no further reaction was observed. [b] The yield quoted is the yield of combined diastereomers **119** and **120** after column chromatography.

Upon subjecting one of the combined oxazolidine **119** and **120** mixtures to HPLC analysis, an improvement in the quality of the chromatogram was observed with greater separation and lower retention time than seen for the precursor **118a/b**. The chromatogram also revealed an increase in ratio between the two oxazolidine diastereomers present with respect to that recorded on the corresponding starting material. This increase in diastereoselectivity suggested that formation of one oxazolidine was favoured, and a similar observation of increased diastereoselectivity was observed by Wagner and Mollath[116] where oxazolidine formation of only one diastereomer from a mixture of two β-amino alcohols resulted under similar reaction conditions, (Figure 46).

Figure 46



By comparing the *anti*- and *syn*-oxazolidines (Scheme 44) it was proposed that the *anti*-derivative **119** has a less strained ring conformation with respect to the *syn*-derivative **120** which may result in faster formation of the former.

To observe the diastereoselective enhancement in more detail - three of the β-amino alcohols mixtures were subjected to identical conditions for oxazolidine formation (2,2-DMP, *p*TSA, DCM, reflux) and subjected to HPLC analysis. The results are illustrated in Table 3.

Table 3

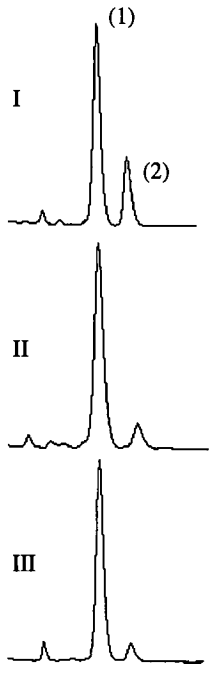
No.	**β-amino alcohol 118a/b origin[a]**	**Ratio[b] of β-amino alcohol 118a/b (Table 1)**	**Yield[c] of 119/120 %**	**Ratio[d] 119:120**
I	Method 4	71:29	86	75:25
II	Method 5	90:10	83	94:6
III	Method 6	86:14	80	91:9

[a]The starting material which resulted from the method as dipicted in Table 1. [b]The ratio is as that reported in Table 1.[c]The yield of combined oxazolidine **119/120** after column chromatography. [d]The ratio of the diastereomers **119/120** was determined by HPLC analysis using the same column and HPLC system as described in Table 1. The column was eluted with 90:10 hexane/IPA at a flow rate of 0.5 ml/min.

The increase in diastereoselectivity is greatest (94:6) in case II which results from the amino alcohol **118a/b** generated from method 5 in the previous section, although both the other two examples also showed an improved ratio of diastereomers after formation of the oxazolidines **119** and **120**. The chromatograms of the resulting oxazolidines I-III are shown in Figure 47.

Unfortunately, efforts to separate the oxazolidine diastereomers by column chromatography failed as a suitable solvent system could not be found that would give sufficient separation of the compounds. Use of preparative HPLC analysis to aid separation was also investigated however an appropriate column could not be found.

Figure 47



I = Oxazolidine mixture resulting from method 4
II = Oxazolidine mixture resulting from method 5
III = Oxazolidine mixture resulting from method 6

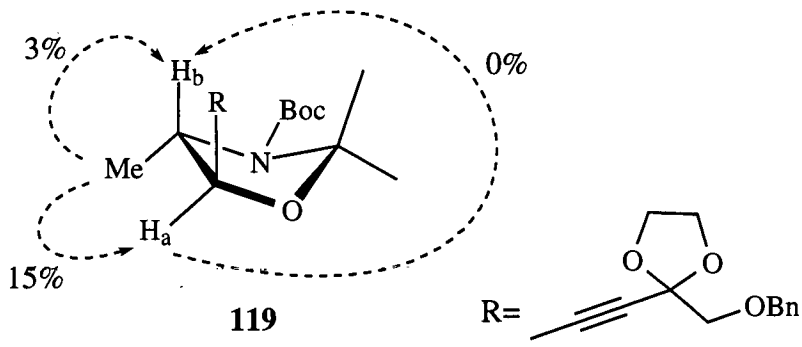
R_t = Peak 1, 18 minutes
Peak 2, 20 minutes

Confirming the configuration of the *anti*-oxazolidine **119**

Due to the increased diastereoselectivity obtained in case II (Table 3) the product from this reaction was subjected to nmr nOe enhancement experiments to determine the configuration at the second stereocentre with respect to the α-methyl group. Figure 48 highlights the percentage enhancements that resulted.

The large enhancement between methyl and H_a (15%) when compared to the small enhancement between methyl and H_b (3%) suggests a strong through space interaction characteristic of a *syn*-relationship. No enhancement was observed between H_b and H_a confirming that the hydrogens H_b and H_a have an *anti*- relationship with respect to each other. Although the minor diastereomer was not available for comparison of the nOe enhancements, these results correlate to those obtained for the *anti*- oxazolidine **56** in the DFJ synthesis.

Figure 48



119

Consequently, it was verified that the major product formed is the *anti*-oxazolidine **119** which in turn results from *syn*-addition of the acetylene **117** to *N*-Boc-L-alaninal **53** in the preceding reaction, as predicted.

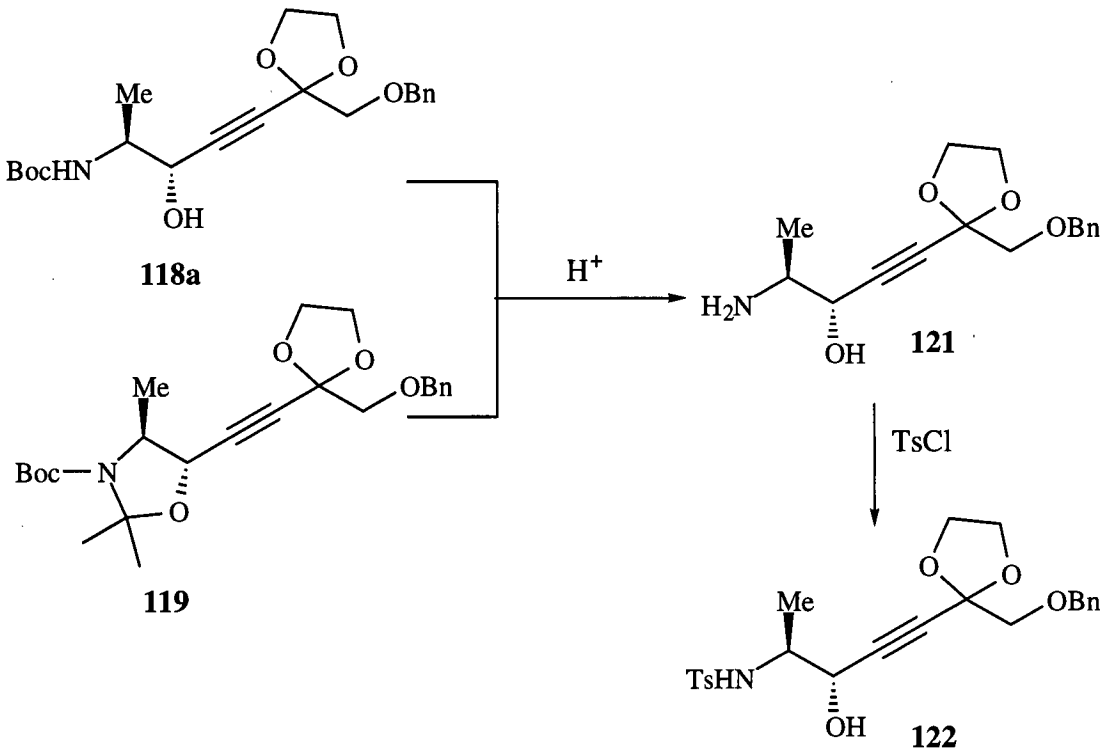
The synthetic pathway was now continued towards the target molecule **27** using the enriched samples of β-amino alcohol **118a** and oxazolidine **119**. Although the nmr spectra of these substrates indicated some signals due to the minor diastereomer, the relative proportion of this diastereomer was negligible and did not hinder assignment of the major diastereomeric products. Therefore, assignment and characterisation of compounds from this point onwards are quoted for the major isomer only, however optical rotations were not obtained on the compounds due to this contamination.

Protecting group manipulation

Removal of the *N*-Boc protecting group was now required to enable *N*-sulfonation to yield the *N*-Tosyl amide. Both β-amino alcohol **118a** and oxazolidine **119** were treated with acidic conditions followed by tosylation conditions in the anticipation of yielding the *N*-Tosyl amide **122**, (Scheme 45).

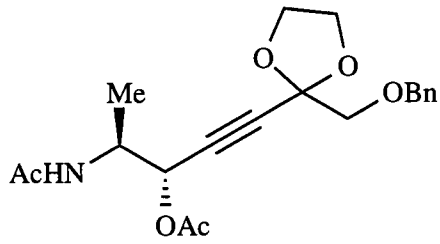
Employment of 3M hydrochloric acid in EtOAc required overnight stirring for both β-amino alcohol **118a** and oxazolidine **119** substrates to be consumed when monitored by tlc, yet neat trifluoroacetic acid or as a 1:1 mixture in DCM was effective in only 30 minutes. ^{1}H nmr spectroscopy was performed on the crude residue obtained from both the methods in the anticipation of obtaining the amine **121**, and although loss of the Boc methyl signals was evident, both spectra were broad and complex. Several repetitions were performed using both sets of conditions but nmr spectra of the crude residues were inconsistent and as a result the signals were difficult to assign.

Scheme 45



Attempts to tosylate the products isolated from the acidic deprotection reactions using tosyl chloride/DMAP/pyridine or tosyl chloride/triethylamine/DCM gave varying mixtures ranging from baseline material to complex mixtures when monitored by tlc. The highest yield obtained of the *N*-Tosyl amide **122** resulted from subjecting the oxazolidine **119** to neat trifluoroacetic acid, removal of the solvent *in vacuo* and treatment of the residue with tosyl chloride and triethylamine in DCM/1,4-dioxane. The amide **122** was isolated in a yield of 32% and was identified by the characteristic methyl and aromatic signals in both ^{1}H and ^{13}C nmr spectra.

To aid confirmation of the intermediate amine **121**, the β-amino alcohol **118a** was subjected to trifluoroacetic acid, the solvent removed under reduced pressure and the residue redissolved in acetic anhydride and pyridine in order to acetylate both the nitrogen and secondary hydroxyl group. After stirring overnight, a complex mixture was observed by tlc but a product was isolated by column chromatography albeit in low yield (18%) and characterised as the diacetylated amino alcohol **123**. The low yield of isolated product and complexity of the mixture observed in this reaction suggested that deprotection of the β-amino alcohol **118a** and oxazolidine **119** was not proceeding to yield the amine as well as had been expected.



123

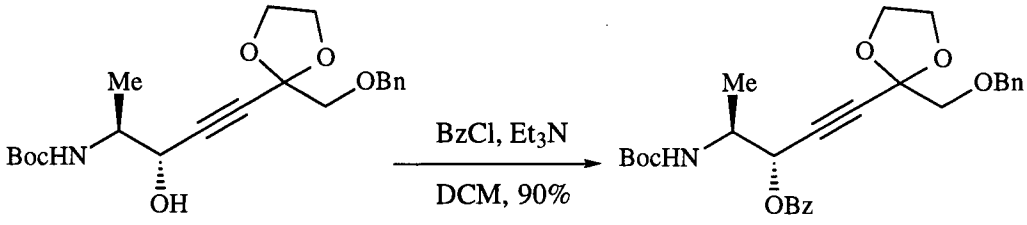
As a result of low formation of the amine **121** it was proposed that protection of the free hydroxyl group may aid the manipulation of nitrogen protecting group by blocking this site and also decreasing the polarity of the corresponding amine.

4.2.4.2 Hydroxyl protection and nitrogen protecting group manipulation

Use of an ester protecting group

A protecting group that would be stable to the acidic conditions of *N*-Boc deprotection was required and after consideration it was decided to mask the hydroxyl group as the benzoyl ester, (Scheme 46). Benzoylation using benzoyl chloride in pyridine/DCM gave low yields of product (45-64%), but the yield was improved significantly by use of benzoyl chloride in triethylamine/DCM under anhydrous conditions (85-90%). The quality of the nmr spectra of the benzoate **124** were significantly improved in comparison to that of the precursor **118a** and also showed very little evidence of the minor diastereomer present.

Scheme 46



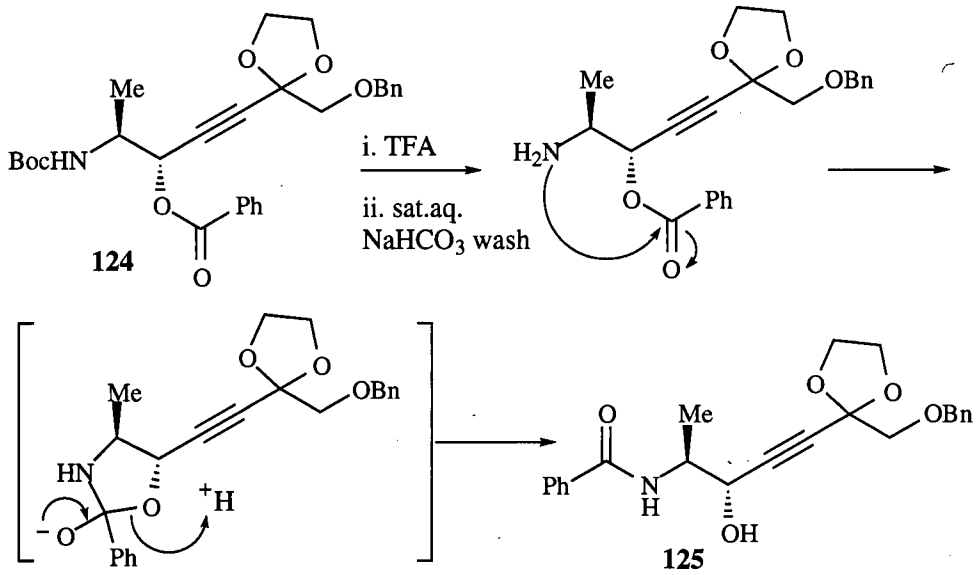
118a **124**

Removal of the *N*-Boc protecting group again proved problematic. Treatment of the benzoate **124** with 3M hydrochloric acid in EtOAc overnight followed by tosyl chloride and triethylamine in DCM resulted in a complex and streaky mixture when visualised by tlc. Reaction with trifluoroacetic acid at 0°C gave baseline material and after removal of the solvent under reduced pressure the residue was taken up in DCM

and washed with sat. aq. $NaHCO_3$ to remove any traces of acid. Two products were isolated after column chromatography.

Nmr spectroscopy performed on the first product verified loss of the methyl signal corresponding to the Boc protons in the ^1H nmr spectrum although initially it was also assumed that the benzoyl ester had been cleaved due to a shift to higher field of the methine signal adjacent to the ester function. This assumption was questioned by an infra-red spectrum which illustrated a carbonyl stretch at 1638 cm^{-1}. After consideration of all the data obtained on the product it was evident that the compound obtained was the benzoyl amide **125** - which is postulated to result from migration of the benzoyl group from the oxygen to the nitrogen by a mechanism illustrated in Figure 49.

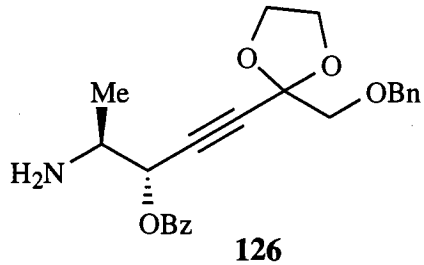
Figure 49



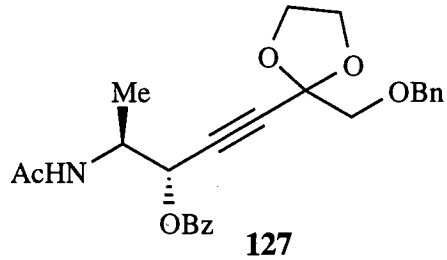
Characteristic data of the benzoyl amide **125** included a broad OH signal in the ^1H nmr spectrum and a sharp doublet at δ 6.41 corresponding to the amide proton. A low frequency carbonyl stretch and broad OH signal were also observed in the infra-red spectrum.

The second product isolated from the reaction mixture also indicated loss of the Boc group in the ^1H nmr spectrum yet suggested that the benzoyl ester was still intact due to very little shift of the adjacent methine doublet observed at δ 5.77 when compared to the precursor **124**. Assignment of this structure was achieved by mass spectral analysis which gave a peak at *m/z* 396 which was confirmed as the MH^+ ion of the free amine **126** by accurate mass giving a formula $C_{23}H_{26}NO_5$. Derivitisation of the amine

126 was performed (Ac_2O/pyridine) yielding the *N*-acetyl amide **127** in 66% yield from the benzoate **124**. Detailed nmr studies were performed on this substrate including a ^1H-^1H COSY spectrum to aid identification.



126



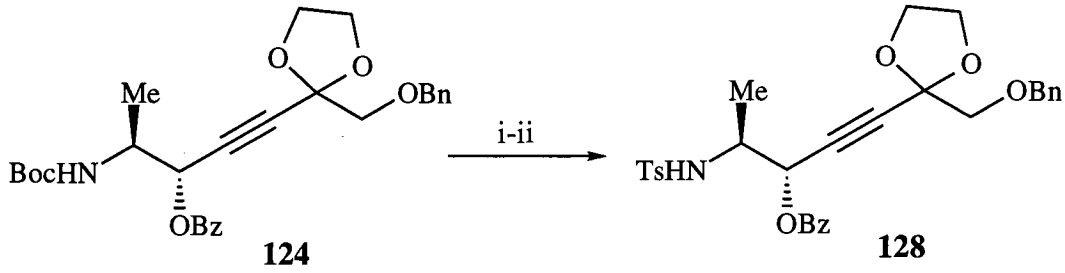
127

Migration of the benzoyl group in **126** was proposed to occur after work up due to production of the free amine, as opposed to the TFA salt, which is then able to undergo the mechanism shown in Figure 49. This postulation was strengthened by observation of some benzoyl migrated product shortly after isolation of the pure amine **126** suggesting migration occurs quite readily in favour of the benzoyl amide **125**.

To prevent such migration, extraction of the product into the organic layer and washing with sat. aq. $NaHCO_3$ was avoided and the trifluoroacetic acid was simply removed *in vacuo* and then subjected to tosylation conditions ($TsCl/Et_3N$/DCM).

Again, two products were isolated from the reaction mixture after column chromatography. The major product (R_F 0.2, hexane/EtOAc 2:1) was identified as the *N*-Tosyl amide **128** and was isolated in a yield of 40%. Characteristic details of the data included the presence of a methyl signal and additional aromatic signals in both ^1H and ^{13}C nmr spectra corresponding to the tosyl group.

Scheme 47

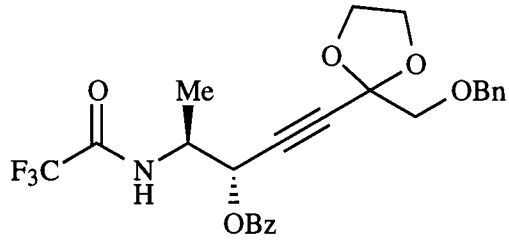


124 **128**

Reagents and conditions: i. TFA. ii. TsCl, Et_3N, DCM, 40% (2 steps).

Assignment of the minor product was not as straightforward. The ^1H nmr spectrum contained proton signals corresponding to all the expected functionality such as an

amine doublet at δ 6.66 (1H), the adjacent benzoate methine at δ 5.71 (1H), the methyl doublet at δ 1.36 (3H), the aromatic protons (10H) and all the functionality in the acetylene unit. ^{13}C nmr spectrum also showed the expected signals however also indicated the presence of two tertiary carbons at δ 156.3 and δ 117.8. After consideration of the reactants and conditions - a ^{19}F nmr spectrum was recorded and highlighted the presence of a fluorine signal at δ -76.2, characteristic of a trifluoroacetate group, and as a result the product was proposed to be the trifluoroacetamide **129**. Nominal and accurate mass spectral analysis confirmed formation of this product with a MH^+ ion peak at *m/z* 492 with the formula $C_{25}H_{25}NO_6F_3$.



129

Attempts to avoid trifluoroacetamide formation by thorough removal of the trifluoroacetic acid including co-evaporation with toluene and chloroform and high vacuum treatment did not significantly reduce the amount of by-product **129** formed after tosylation.

A final attempt to avoid formation of the trifluoroacetamide **129** by deprotection with 3M hydrochloric acid in EtOAc followed by the similar tosylation conditions only gave the *N*-Tosyl amide **128** in 25% yield.

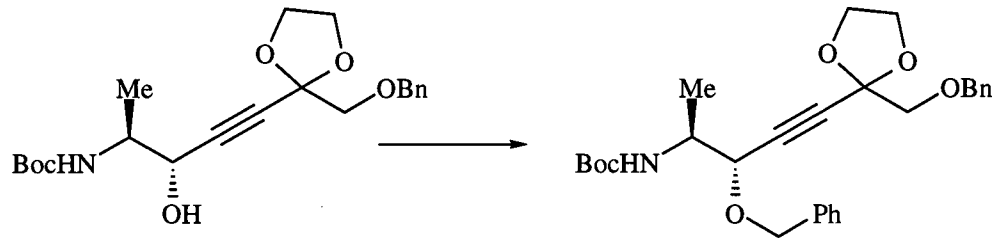
Use of an ether protecting group

It was anticipated that protection of the hydroxyl group as an ether would avoid the problem of benzoyl migration on formation of the corresponding amine.

Protection as the benzyl ether (Scheme 48) was targeted due to its stability under acidic and basic conditions, and could be cleaved simultaneously with the primary benzyl ether later in the synthesis. The use of benzyl bromide and silver (I) oxide in refluxing ether[102] as used in the previous benzyl ether formation, gave very little of the desired product **130** (8%) along with recovered starting material **118a**. Product formation

was evident due to the presence of two doublets in the ^1H nmr spectrum due to the diastereotopic protons in the newly formed benzyl group and also the increased number of aromatic protons.

Scheme 48

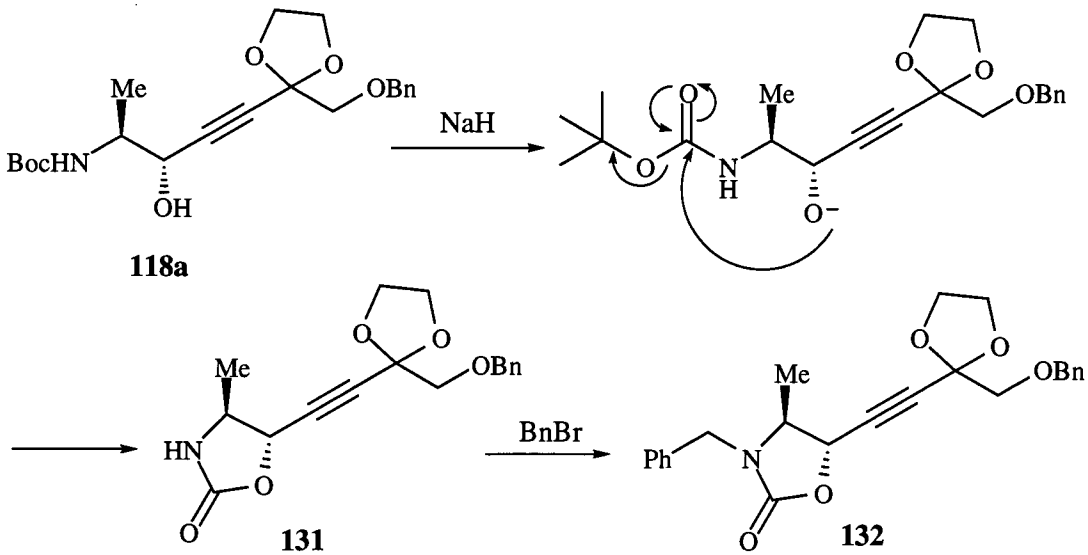


118a **130**

Reagents and conditions: BnBr, Ag_2O, ether, reflux, 8%. or BnBr, NaH, DMF, 17%.

Subjecting the β-amino alcohol **118a** to benzyl bromide with sodium hydride in DMF again gave only a small quantity of benzyl ether (17%) and what was thought to be recovered starting material. Surprisingly, the ^1H nmr spectrum of the recovered starting material did not show any resemblance to that of the β-amino alcohol **118a** but illustrated a much simplified spectrum with no Boc group and convergence of the aromatic signals into a broad singlet. The infra-red spectrum illustrated an unexpectedly high carbonyl stretch at 1759 cm^{-1} and the ^{13}C nmr spectrum also confirmed the presence of a carbonyl with a tertiary carbon peak at δ 155.6. After consideration of the reaction conditions and the data obtained on the isolated product the following mechanism was proposed for the formation of an oxazolidinone **132**, (Figure 50).

Figure 50

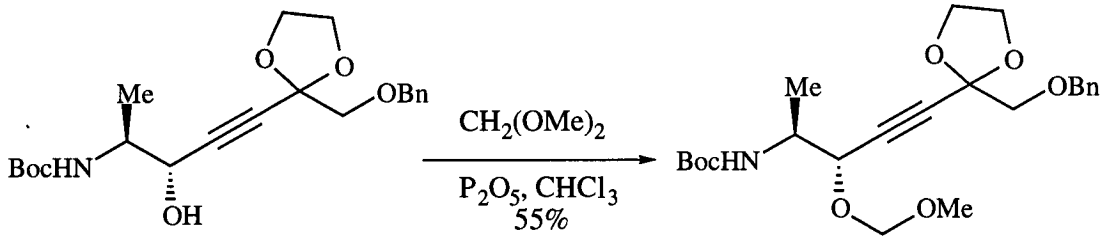


118a **131** **132**

It was proposed that the removal of the hydroxyl proton by sodium hydride results in the alkoxy anion which then attacks the carbonyl of the Boc group with subsequent loss of *tert*-butyl alcohol to give the oxazolidinone **131**. In the presence of sodium hydride and benzyl bromide this can then undergo benzylation on the nitrogen to give the *N*-benzyl oxazolidinone **132**.

Due to the unsuccessful formation of the benzyl ether, a different ether protecting group was chosen - methoxymethyl (MOM-ether). Although this group is cleaved by harsh acidic hydrolysis, colleagues found that MOM ethers derived from secondary alcohols survived conditions of trifluoroacetic acid for up to 1 hour without significant cleavage. Formation of the MOM ether of the β-amino alcohol **118a** could not be effected in the presence of sodium hydride due to problems of proton abstraction and rearrangement to the oxazolidinone **132** hence an attempt using methoxymethyl chloride and dimethylaniline in DCM was implemented but this resulted only in starting material after overnight stirring. Treatment of the β-amino alcohol **118a** with dimethoxymethane in the presence of phosphorous pentoxide in chloroform[117] did yield the MOM ether **133** albeit in moderate yield (55%). (Scheme 49).

Scheme 49



118a **133**

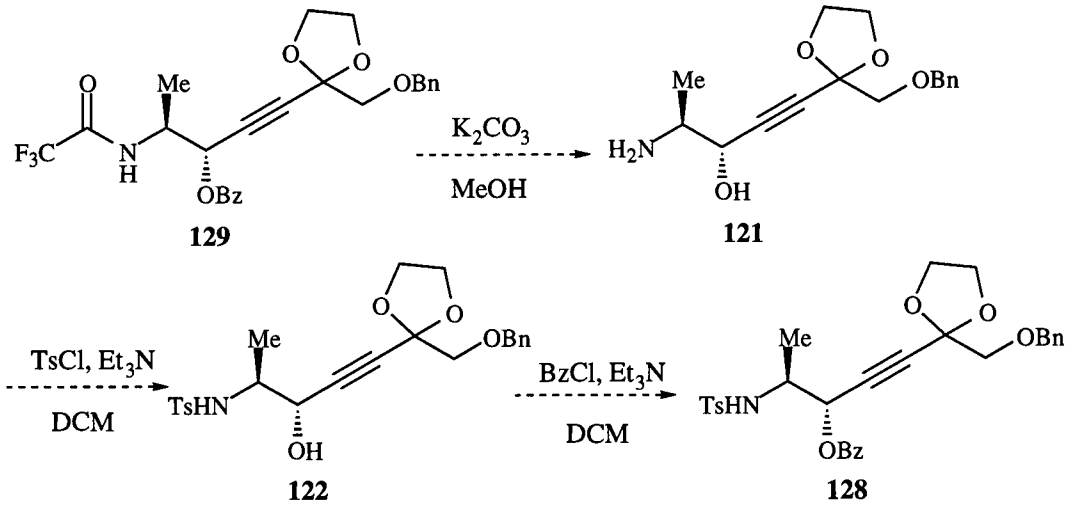
Unfortunately, treatment of the MOM ether **133** with trifluoroacetic acid followed by tosylation conditions (TsCl, Et_3N, DCM) gave a multispot mixture when visualised by tlc and due to the complexity and the various side reactions that could result from cleavage of the MOM protecting group no purification was performed.

Conclusion

Although the *N*-tosyl amide **128** was formed from the benzoate **124** the yield was only moderate. A potential way of increasing the overall yield of *N*-tosyl amide **128** could be performed by 'recycling' the by-product trifluoroacetamide **129**, (Figure 51).

Trifluoroacetamides are cleaved by potassium carbonate in methanol, however under these conditions the benzoyl ester would also be cleaved thus forming the amine **121**. Theoretically this could be subjected to *N*-tosylation followed by benzoylation of the secondary alcohol to yield the *N*-tosyl amide **128**. Although this involves several steps, at this stage in the synthesis it would allow more material to be available for continuation in the synthesis.

Figure 51



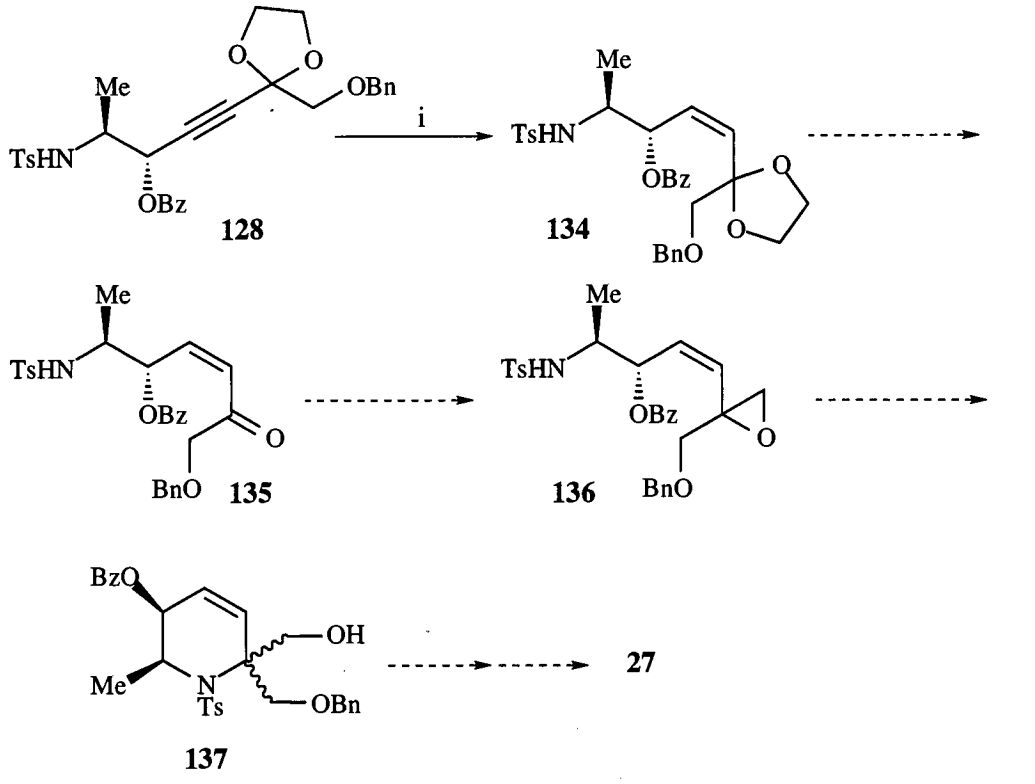
129 **121** **122** **128**

Due to time constraints, this sequence was not implemented and the synthesis was continued from the *N*-tosyl amide **128** to attempt further functionalisation and ring closure.

4.2.5 Continuation of the synthesis:- Functional group modification

Due to the lack of time and material it was reasoned that manipulation of the *N*-Tosyl amide **128** to the epoxide **136** would align the system for a 6-*exo-tet* cyclisation to form the piperidine ring **137** as outlined in Scheme 50. Reduction of the acetylene unit of the *N*-Tosyl amide **128** to the *Z*-alkene **134** was effected by hydrogenation in the presence of the Lindlar catalyst in EtOAc-hexane in moderate yield (68%). Formation of the *Z*-alkene was evident in the ^{1}H nmr spectrum which illustrated a coupling constant *J* 8.0 Hz between the olefin protons, a characteristic value for *Z*-alkenes.

Scheme 50

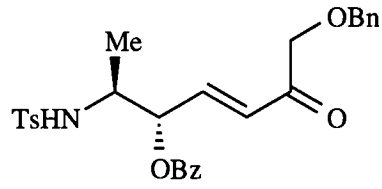


Reagents and conditions: i. Lindlar catalyst (Pd on $CaCO_3$), H_2, EtOAc-hexane, 68%.

The next step in the synthesis involved removal of the 1,3-dioxolane protecting group to yield the *Z*-enone **135** which is usually achieved under acidic catalysed hydrolysis. Considering no significant hydrolysis of the acetal under the acidic conditions of *N*-Boc deprotection was observed previously it was anticipated that removal of the acetal may prove problematic.

The first endeavour to remove the acetal group was using neutral, anhydrous conditions following a procedure by Kerr and co-workers[118] with triphenylphosphine and carbon tetrabromide in DCM. Kerr reported the deprotection of a range of aliphatic and aromatic acetals and ketals including an *E*-α,β-unsaturated-1,3-dioxolane using one set of conditions, hence the α,β-unsaturated ketal **134** was subjected to the reported procedure. A complex mixture resulted from the reaction and only one product was isolated in significant quantity. This product was subjected to high field nmr spectroscopy and from the spectra it was evident that the 1,3-dioxolane had been cleaved due to the loss of the corresponding signals. The signals resulting from the alkene protons in the ^1H nmr had also shifted to higher field due to the conjugation with the resulting carbonyl but unfortunately these alkene signals illustrated a large

coupling constant with a value of *J* 16.0 Hz when compared to that observed in the precursor **134** (*J* 8.0 Hz). This large coupling is more characteristic for *E*-alkenes than for *Z*- and as a result it was proposed that the product isolated from this reaction mixture was the *E*-enone **138** resulting from isomerisation of the double bond in the reaction.



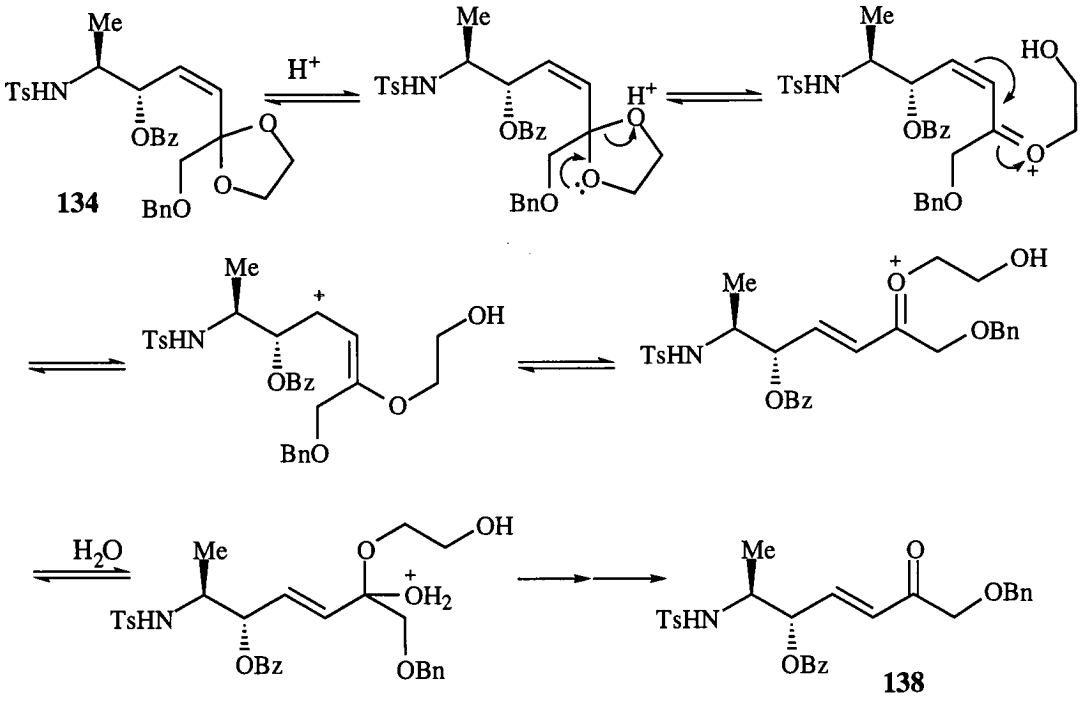
138

Hydrolysis of the 1,3-dioxolane of the α,β-unsaturated ketal **134** was also attempted using 80% acetic acid at 65°C,[119] but after column chromatography the *E*-isomer **138** was again isolated in 51% yield. A final attempt using the activated clay montmorrillonite K10 in DCM by adapting a procedure by Taylor *et al.*,[120] again led to the *E*-isomer.

The *E*-alkene formation was unexpected and there is no literature precedent on the removal of 1,3-dioxolane groups of *Z*-acyclic α,β-unsaturated ketals. However it is well documented that mono-substituted *Z*-alkenes readily undergo isomerisation to the corresponding *E*-isomers under various conditions including acid catalysis.[121] A proposed mechanism for the *E*-alkene **138** formation is illustrated in Figure 52, and proposes that isomerisation to the more stable *E*-isomer occurs during the cleavage of the ketal in **128** *via* the enol cation.

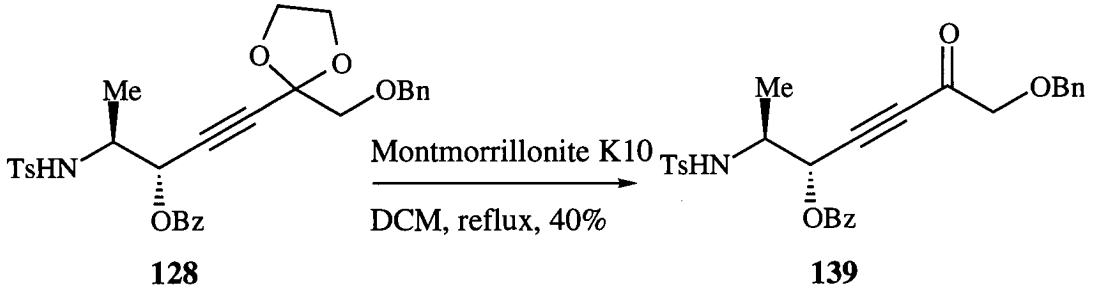
This resulting *E*-isomer **138** is unsuitable for piperidine ring formation due to the wrong configuration of the double bond, thus a different approach to the *Z*-enone **135** was undertaken by simply reversing the order of the two steps above. Removal of the 1,3-dioxolane in the α,β-acetylenic ketal **128** was performed first to avoid any isomerisation of the double bond, (Scheme 51).

Figure 52

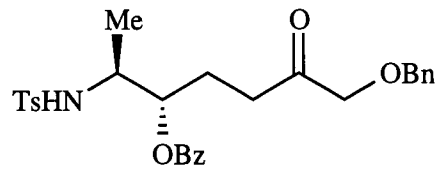


Use of 80% acetic acid at 65°C for 26 hours only resulted in recovered starting material, but treatment of **128** with montmorrillonite K10 yielded the α,β-acetylenic ketone **139** in 40% yield although a large amount of K10 was used compared to that suggested by Taylor.[120]

Scheme 51



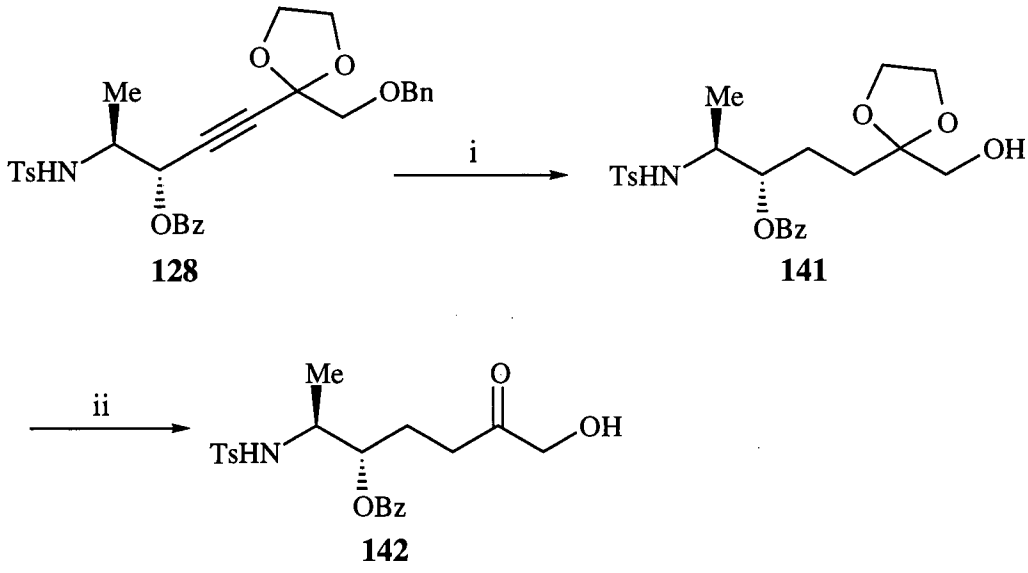
Due to the small amount of material remaining at this stage only one attempt to reduce the acetylene to the *Z*-enone **135** using hydrogenation conditions in the presence of the Lindlar catalyst was effected. Unfortunately, the product isolated did not indicate the presence of any olefin protons and it was suggested from the ^{1}H and ^{13}C nmr spectra that the product was that resulting from over reduction of the acetylene to the saturated ketone **140**.



140

Finally, a second approach that ran parallel to the above sequence is illustrated in Scheme 52. Reduction of the acetylene in **128** to the alkane **141** was effected by hydrogenation in the presence of palladium on carbon in EtOAc-hexane to give the alkane in 51% yield. The alkane **141** was subjected to montmorrilonite K10 in DCM however this resulted in very little isolated product. A ^{1}H nmr spectrum did suggest cleavage of the 1,3-dioxolane to give the ketone **142**, but was complex due to contamination and no further data was collected.

Scheme 52



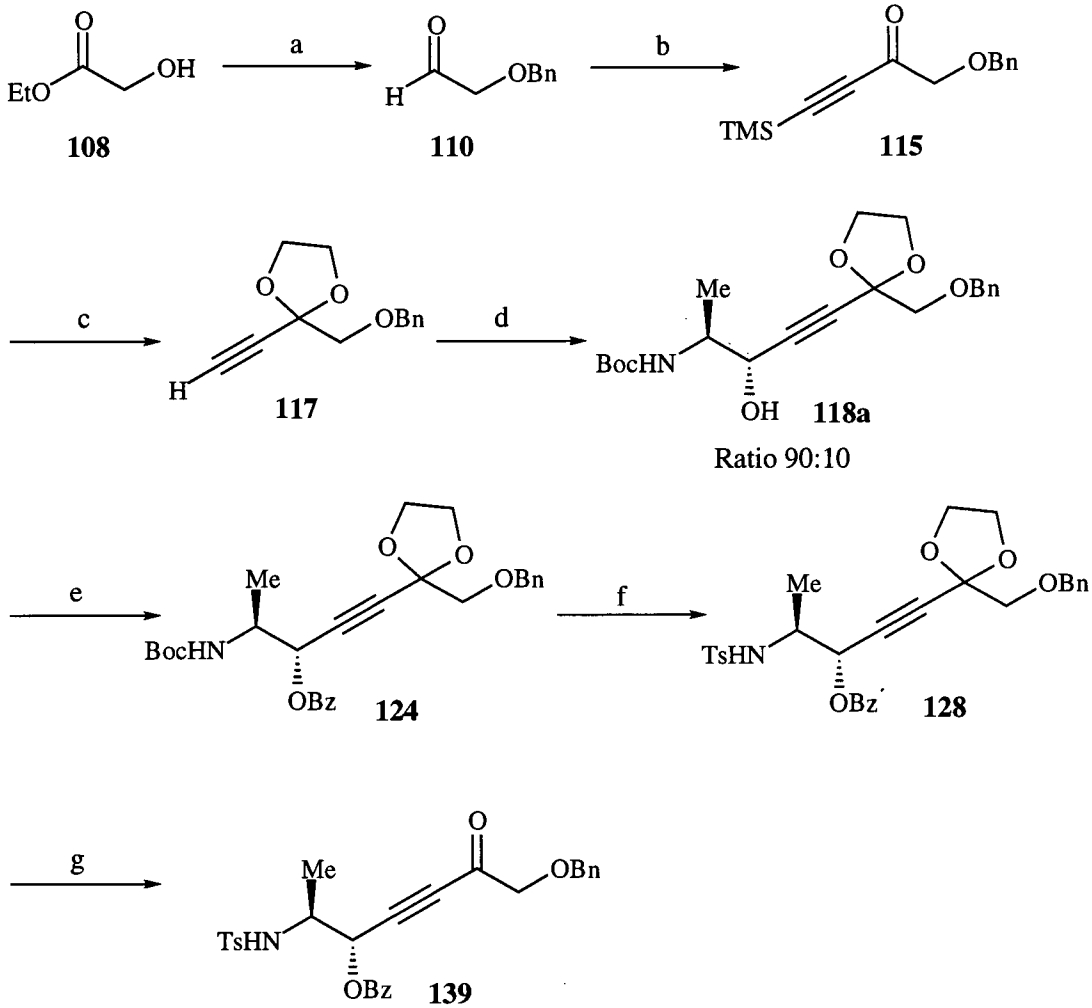
128 **141** **142**

Reagents and conditions: i. Pd-C, H_2, EtOAc, Hexane, 51%. ii. Montmorrillonite K10, DCM.

4.3 SUMMARY OF CHAPTER 4

Eleven steps have been completed *en route* to the key target molecule 1,1-*bis*-hydroxymethyl-1,5-dideoxy-1,5-imino-L-fucitol **27** and these are outlined in Scheme 53. Good to excellent yields were obtained in the initial steps on moderate scale allowing sufficient material to be utilised for investigation of the β-amino alcohol **118** formation. Suitable conditions were found for this reaction step by differing the conditions and thus resulted in the desired β-amino alcohol **118a** as the major diastereomer in favorable diastereoselectivity. Conversion of the β-amino alcohol **118a** to the corresponding oxazolidine **119** confirmed the absolute stereochemistry by nmr experiments.

Scheme 53



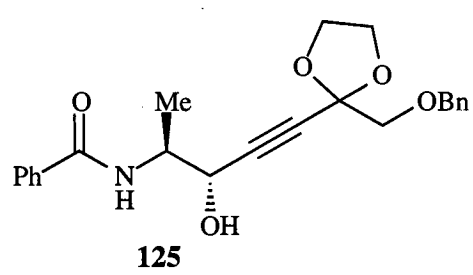
Reagents and conditions: (a) i. BnBr, Ag_2O, ether, reflux, 82%. ii. DIBAL (1M in toluene), DCM, -78°C, 60%. (b) i. *Bis*-trimethylsilyl acetylene, MeLi:LiBr, THF, 0°C,

75%. ii. TEMPO, NaOCl, BTAC, NaBr, sat. aq. $NaHCO_3$, sat. aq. NaCl, DCM, 0°C, 97%. (c) i. $HOCH_2CH_2OH$, TMS-Cl, DCM, 88%. ii. K_2CO_3, MeOH, 93%. (d) EtMgBr, **53**, -78°C, 59%. (e) BzCl, Et_3N, DCM, 90%. (f) i. TFA. ii. TsCl, Et_3N, DCM, 40% (2 steps). (g) Montmorrillonite K10, DCM, reflux, 40%.

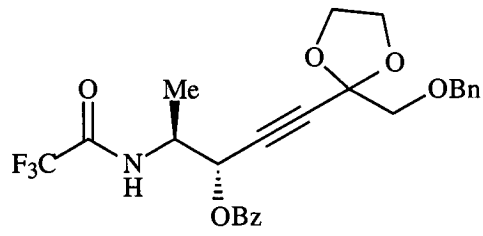
Continuation from the β-amino-alcohol **118a** traversed several pathways in an attempt to find an appropriate hydroxyl protecting group yet the first choice of the benzoyl ester **128** proved the most successful.

Although various reactions gave low yields of desired products, the by-products from these reactions were identified and are illustrated in Figure 53. These unwanted products might be converted into more useful intermediates if considered in more detail.

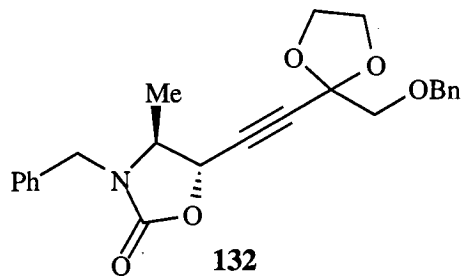
Figure 53



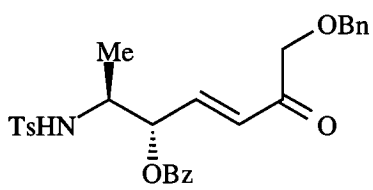
125



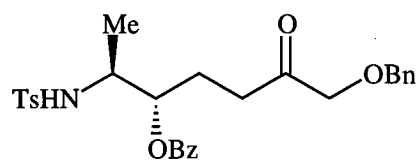
129



132



138



140

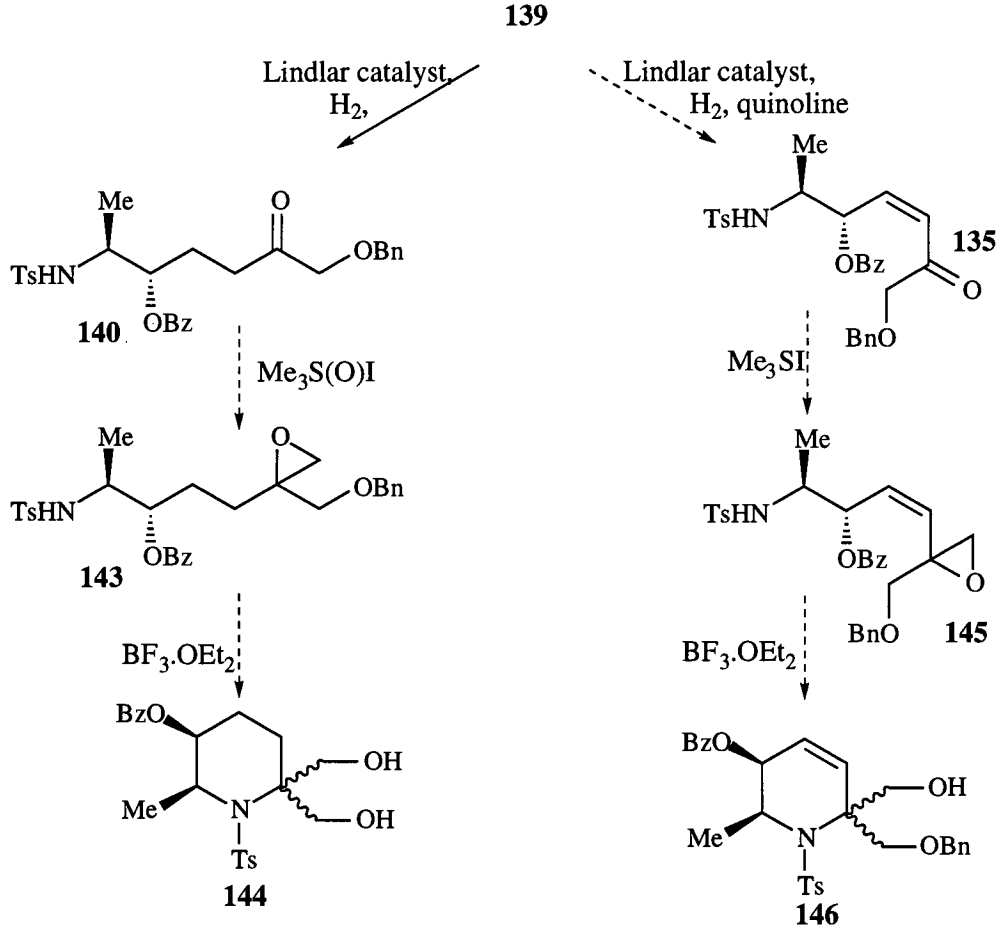
4.4 FUTURE WORK

4.4.1 Synthesis of analogues to investigate the 6-*exo-tet* cyclisation

To enable the 6-*exo-tet* cyclisation of the *N*-tosyl protected nitrogen onto the epoxide to be investigated, it is proposed that a semi-functionalised *N*-tosyl amide be prepared before introducing the remaining stereochemistry. This can be approached by several pathways as outlined below by continuation from where the research ended.

Although problems were encountered in the conversion of the 1,3-dioxolane to the corresponding ketone, the α,β-acetylenic ketone **139** was isolated in 40% yield yet this yield could be improved by further investigation of cleavage conditions. Lindlar catalysed hydrogenation of the α,β-acetylenic ketone **139** unexpectedly yielded the over-reduced alkane **140**, however this could be converted to the epoxide **143** and subjected to boron trifluoride etherate to give the piperidine analogue **144**, (Scheme 54).

Scheme 54

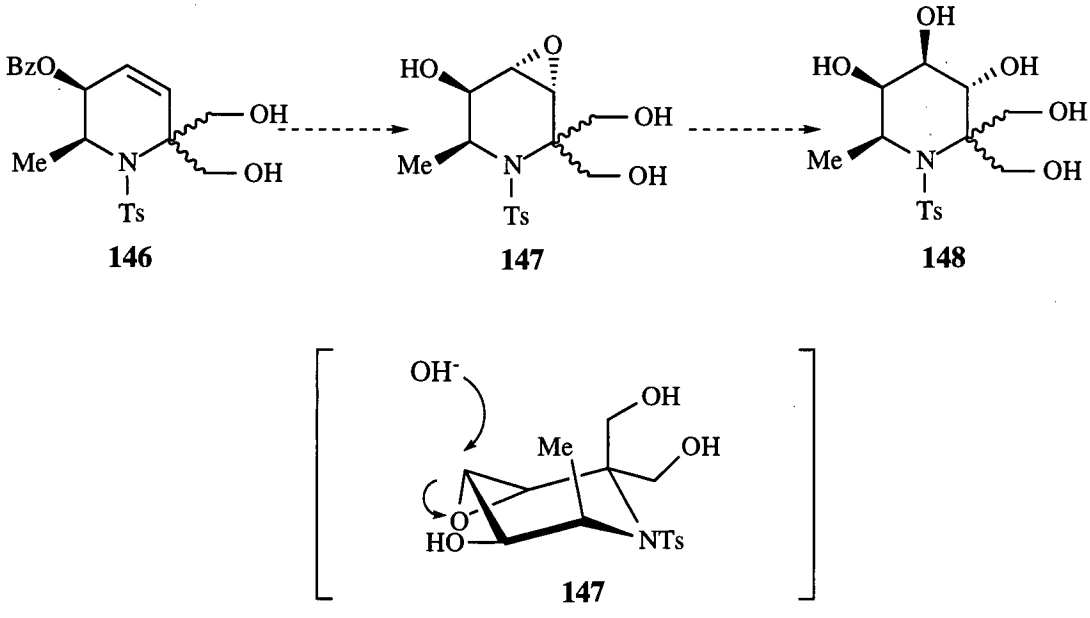


Alternatively, if a similar Lindlar catalysed hydrogenation of the acetylene in **139** is performed in the presence of quinoline this may prevent over reduction and hence result in the Z-enone **135**. Epoxidation of the carbonyl utilising an appropriate sulfur ylide followed by boron trifluoride etherate mediated cyclisation is expected to afford the piperidine **146**.

4.4.2 Functionalisation of the piperidine 146 to yield the target molecule 27

Successful formation of the piperidine analogue **146** would then allow the hydroxyl groups to be incorporated by an acid or base catalysed ring opening of an appropriate epoxide. It is reasoned that formation of the epoxide **147** will allow regioselective ring opening *via* the favoured *trans*-diaxial opening to yield the desired stereochemistry as in **148**, (Scheme 55). Removal of the N-protecting group would then produce the target molecule **27**.

Scheme 55



5. EXPERIMENTAL

5.1 GENERAL

Infrared spectra were recorded as thin films either using sodium chloride plates or by use of disposable IR cards (3M, type 61, polyethylene 19mm aperture) and are denoted as (film, NaCl) or as (film, IR card) respectively. Solids were recorded as KBr discs and in other cases in solution, and were performed on a Perkin Elmer 881 Infra-red spectrophotometer or a Perkin Elmer Paragon 1000 FT-IR, frequencies being measured in wavenumbers (cm^{-1}).

Nmr spectra were recorded on either a Varian Gemini 2000 (200 MHz, ^1H; 50.1 MHz, ^{13}C), a Brucker AC 250 (250 MHz, ^1H; 62.9 MHz, ^{13}C), a Brucker AC 300 (300 MHz, ^1H; 75.5 MHz, ^{13}C), a Brucker WH 360 (360 MHz, ^1H; 90.6 MHz, ^{13}C), a Brucker AM 400 (400 MHz, ^1H; 100.6 MHz, ^{13}C), or a Varian Inova 600 (600 MHz, ^1H) spectrometer. ^1H chemical shifts in $CDCl_3$, CD_3OD and D_2O are referenced with respect to residual $\mathbf{CH}Cl_3$, $\mathbf{CH}D_2OD$ and **H**OD respectively, for ^{13}C spectra in $CDCl_3$ and CD_3OD chemical shifts are referenced to $\mathbf{C}DCl_3$ and $\mathbf{C}D_3OD$ respectively. Spin coupling constants (*J*) are given in Hertz (Hz) and are rounded up to the nearest 0.5 Hz, and the chemical shift quoted in parts per million (ppm). The following abbreviations are used in assignment of the nmr spectra: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dt, double triplet; ddd, double doublet of doublets; m, multiplet; br, broad.

Optical rotations were recorded on an AA-1000 polarimetry with a cell path length of 0.5 dm and concentations (c) quoted in g/100 ml (measurements taken at 589 nm). $[\alpha]_D^T$ values are given in 10^{-1} deg cm^2 g^{-1}. Optical rotations are recorded only on the compounds that were isolated as single isomers and not on inseparable mixtures or impure compounds.

Fast Atom Bombarbment (F.A.B.) mass spectra were recorded on a Kratos MS50TC instrument and Electron Impact (E.I.) spectra on a Finnigan 4600 instrument. Chemical ionisation (C.I.) mass spectra were recorded on a VG Biotech Quattro II spectrometer (low resolution) and a VG ZAB-E spectrometer (high resolution) at the EPSRC Mass Spectrometry Service, University of Wales, Swansea, (no percentage enhancements were quoted for these samples). Values are quoted as *m/z* values.

Elemental analysis (CHN) was performed on a Perkin Elmer 2400 CHN Elemental Analyser.

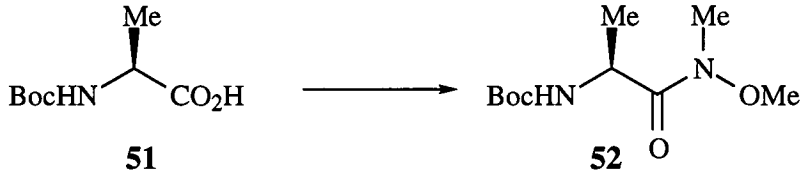
Melting point determinations were recorded on an Electrothermal Melting Point apparatus and are given in (°C) uncorrected.

Thin layer chromatography (tlc) was performed on Merck $60F_{254}$ (0.25 mm) glass backed silica gel plates. The plates were visualised by UV fluorescence, or by heating after treatment with solutions of an acidic soution of ninhydrin or alkaline solution of potassium permanganate ($KMnO_4$). Column chromatography was performed using Merck silica gel 60H (230-400 mesh) and eluant systems are quoted in volume ratios.

Reactions which required anhydrous conditions were performed under an atmosphere of nitrogen or argon using glassware dried in an oven (T 150°C for at least 5 hours). Solvents tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl before use, and DCM was distilled from calcium hydride, or otherwise purchased directly from Aldrich. Pyridine was also distilled from calcium hydride, and stored over potassium hydride under a nitrogen atmosphere. Petroleum ether 40/60 (referred to as petrol) was distilled prior to use and all other solvents and reagents were supplied by commercial suppliers. Brine refers to a saturated solution of sodium chloride.

5.2 Experimental For Chapter 3. The Synthesis Of L-Deoxyfuconojirimycin

5.2.1 N-(tert-*butoxycarbonyl*)-L-*alanine* N-*methoxy*-N-*methylamide* **52**

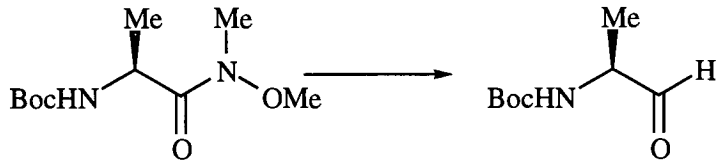


51 **52**

A stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (10.7 g, 0.11 mol) in DCM (70 ml) under nitrogen was cooled to 4°C. *N*-Methylpiperidine (13 ml, 0.21 mol) was added and the resulting solution of free *N,O*-dimethylhydroxylamine was stirred at 4°C until required.

N-Boc-L-alanine **51** (20.0 g, 0.11 mol) was dissolved in THF (200 ml) and DCM (100 ml) under nitrogen and cooled to -42°C. *N*-Methylpiperidine (13 ml, 0.11 mol) was added rapidly to the stirred solution and the temperature allowed to rise to -12°C where it was stabilised using an ice-methanol bath. Methyl chloroformate (8.5 ml, 0.11 mol) was added and after 2 minutes the solution of free *N,O*-dimethyl hydroxylamine added and the mixture allowed to warm to room temperature. After 21 hours the resulting solution was cooled to -5°C and washed with 0.2M HCl (2 x 200 ml), 0.5M NaOH (2 x 250 ml) and brine (250 ml). The organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the resulting solid recrystallised from EtOAc-petrol to give the *Weinreb amide*[70] **52** as white crystals (19.72 g, 78%). mp 146-148°C; R_F (hexane-EtOAc 1:1) 0.32; $[\alpha]_D^{24}$ -27.58 (*c* 0.99 in MeOH); (Found: C, 51.80; H, 8.82; N, 12.05; $C_{10}H_{20}N_2O_4$ requires C, 51.71; H, 8.68; N, 12.06%); υ_{max}/cm^{-1} ($CHCl_3$) 3488-3683 (NH), 1705 (C=O urethane), 1661 (C=O amide); δ_H (300 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.0, CH*Me*), 1.44 (9H, s, OC*Me*$_3$), 3.20 (3H, s, N*Me*), 3.76 (3H, s, O*Me*), 4.60-4.74 (1H, m, C*H*Me) and 5.13-5.29 (1H, br s, N*H*CH); δ_C (62.9 MHz, $CDCl_3$) 18.6 (CH_3, CH*Me*), 28.3 (CH_3, OC*Me*$_3$), 32.2 (CH_3, N*Me*), 46.5 (CH, *C*HMe), 61.5 (CH_3, O*Me*), 79.4 (C, O*C*Me$_3$), 155.1 (C, *C*=O urethane) and 173.3 (C, *C*=O amide); *m/z* (F.A.B.) 233 [$(MH)^+$, 78.9%], 159 (50), 116 (53), 57 (100); [Found: $(MH)^+$, 233.14906. $C_{10}H_{21}N_2O_4$ requires MH, 233.15013].

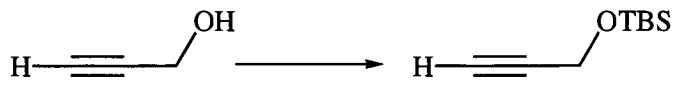
5.2.2 N-(tert-*butoxycarbonyl)-L-alaninal 53*



52 **53**

Lithium aluminium hydride (1M solution in ether, 118 ml, 0.12 mol), was added to ether (50 ml) and stirred for 30 minutes under a nitrogen atmosphere. The solution was cooled to -60°C and a solution of the Weinreb amide **52** (25.31 g, 0.11 mol) in THF (300 ml) and DCM (100 ml) added dropwise over 45 minutes, whereafter the reaction was allowed to warm to 5°C. The reaction mixture was cooled to -60°C and quenched by slow addition of 30% aq. $KHSO_4$ solution (50 ml) and the resulting white suspension stirred at room temperature for 2 hours then filtered through a plug of Celite and washed with ether (2 x 100 ml). The ether liquors were washed with cold 1M HCl (2 x 100 ml), sat. aq. $NaHCO_3$ (2 x 100 ml), brine (100 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* yielded the *α-amino aldehyde*[70] **53** as a white solid (15.47 g, 82%), mp 90-92°C; R_F (hexane-EtOAc 2:1) 0.30; υ_{max}/cm^{-1} (KBr disc) 3341-3682br (NH), 1728 (C=O, aldehyde), 1700 (C=O, urethane), 1250, 1033 (C-O); δ_H (250 MHz, $CDCl_3$) 1.32 (3H, d, *J* 7.0, CH*Me*), 1.45 (9H, s, OC*Me*$_3$), 4.12-4.33 (1H, br.m, C*H*Me$_3$), 5.00-5.19 (1H, br.s, N*H*) and 9.55 (1H, s, C*H*O); δ_C (50.1 MHz, $CDCl_3$) 13.3 (CH_3, CH*Me*), 26.8 (CH_3, OC*Me*$_3$), 54.1 (CH, *C*HMe), 78.6 (C, O*C*Me$_3$), 154.0 (C, *C*=O urethane) and 198.6 (C, *C*=O aldehyde); *m/z* (E.I.) 173 (M^+, 0.1%), 172 (1), 144 (28), 88 (31), 57 (100); (Found: M^+, 173.10467. $C_8H_{15}NO_3$ requires M, 173.10519).

5.2.3 *1-(*tert-*butyldimethylsilyloxy)prop-2-yne 54*

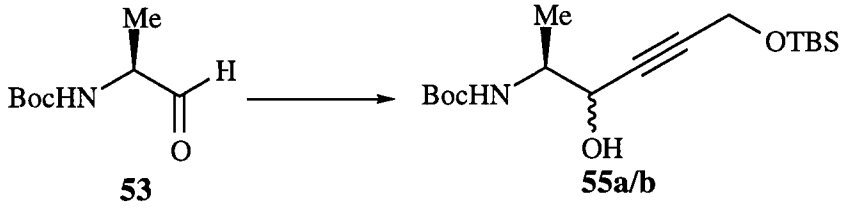


54

Solid *tert*-butyldimethylsilylchloride (19.80 g, 0.13 mol) was added to a stirred solution of imidazole (1.62 g, 0.02 mol) in pyridine (50 ml) under a nitrogen atmosphere. Propargyl alcohol (6.65 g, 0.12 mol) was added and the mixture stirred at room temperature for 5 hours and the resulting precipitate filtered and washed with ether (10 ml). The organic extract was washed with dilute HCl (2 x 25 ml), brine (20

ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to give the *TBS ether* **54** as a colourless oil (16.56 g, 82%) at 21°C/0.1 mm Hg. R_F (petrol-EtOAc, 4:1) 0.86; υ_{max}/cm^{-1} (film, NaCl) 3313 (CH acetylene), 1256 ($SiMe_3$), 1098 (C-O), 837 ($SiMe_3$); δ_H (250 MHz, $CDCl_3$) 0.11 (6H, s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 2.36 (1H, t, *J* 2.0, C*H*-acetylene) and 4.28 (2H, d, *J* 2.0, C*H*$_2$OSi); δ_C (62.9 MHz, $CDCl_3$) -5.3 (CH_3, Si*Me*$_2$), 18.2 (C, O*C*Me$_3$), 25.7 (CH_3, SiC*Me*$_3$), 51.4 (CH_2, *C*H$_2$OTBS), 72.7 (C, *C*-acetylene) and 82.4 (CH, *C*H-acetylene); *m/z* (F.A.B.) 171 [$(MH)^+$, 69.7%], 131 (22), 115 (33); [Found; $(MH)^+$ 171.12108. $C_9H_{19}OSi$ requires MH, 171.12052].

5.2.4 (2S, 3RS)-N-(tert-butoxycarbonyl)-2-amino-6-(tert-butyldimethylsilyloxy)-3-hydroxyhex-4-yne ***55a/b***

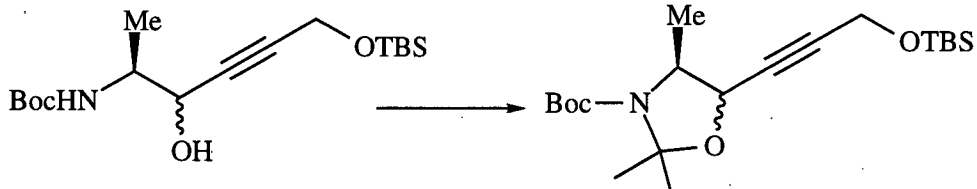


53 **55a/b**

A solution of 1-(*tert*-butyldimethylsilyloxy)prop-2-yne **54** (25.20 g, 0.15 mol) in ether (50 ml) under an atmosphere of nitrogen was cooled to 0°C and methylmagnesium iodide (3M in ether, 50.0 ml, 0.15 mol) added. The resulting solution was stirred at 0°C for 5 minutes and heated under reflux for 14 hours whereafter it was allowed to cool to room temperature before the dropwise addition to a cooled (-78°C) stirred solution of *N*-Boc-L-alaninal **53** (11.85 g, 0.68 mol) in ether (100 ml) under an atmosphere of nitrogen. The solution was warmed to room temperature and stirred for 1 hour before quenching by slow addition of sat. aq. NH_4Cl solution (100 ml). The layers were separated and the organic phase washed with brine (100 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue was subjected to column chromatography eluting with petrol-EtOAc (4:1) to yield an inseparable mixture of the *β-amino alcohols*[68] **55a/b** (14.70 g, 62%), R_F 0.35; δ_H (250 MHz, $CDCl_3$) 0.10 (6H, s, Si*Me*$_2$), 0.90 (9H, s, SiC*Me*$_3$), 1.21 (3H, ov.d, CH*Me* diastereomers), 1.42 (9H, s, OC*Me*$_3$), 3.00-3.40 (1H, br.s, O*H* diastereomers), 3.60-4.00 (1H, br.m, C*H*Me diastereomers), 4.33-4.50 (3H, m, C*H*OH and C*H*$_2$OTBS) and 4.51-4.80 (1H, ov.d, N*H* diastereomers); δ_C (62.9 MHz, $CDCl_3$) -5.2 (CH_3, Si*Me*$_2$), 16.0, 16.2 (CH_3, CH*Me* diastereomers), 18.2 (C, OSi*C*Me$_3$), 25.8, 28.3 (CH_3, SiC*Me*$_3$ and OC*Me*$_3$), 50.7, 51.2 (CH, *C*HMe

diastereomers), 51.6 (CH_2, CH_2OTBS), 65.9, 66.3 (CH, CHOH diastereomers), 79.8, 79.9, 82.5, 83.0, 84.6, 85.0 (3xC, 2x*C*-acetylene and O*C*Me$_3$ diastereomers) and 155.8 (C, *C*=O).

5.2.5 (4S, 5SR)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[3-(tert-butyldimethylsilyloxy)prop-1-yn-1-yl]oxazolidine ***56/57***

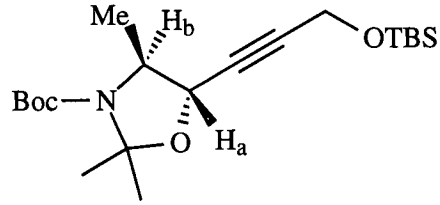


55a/b **56/57**

The diastereomeric mixture of the β-amino alcohols **55a/b** (14.76 g, 43.0 mmol) was dissolved in acetone (150 ml) and 2,2-dimethoxypropane (50 ml) and boron trifluoride etherate (0.3 ml) were added and the solution stirred for 8 hours at room temperature. The solvent was removed under reduced pressure, diluted with DCM (100 ml) and washed with sat. aq. $NaHCO_3$ (2 x 100 ml), water (2 x 100 ml) and brine (100 ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield an oily residue which was subjected to several column chromatography steps eluting with petrol-ether (12:1) to afford the *anti*-**56** (7.92 g, 48%) and the *syn*-**57** (3.31 g, 20%) oxazolidine diastereomers as colourless oils.

(4*S*, 5*S*)-*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[3-(*tert*-butyldimethylsilyl oxy)prop-1-yn-1-yl]oxazolidine **56**: R_F 0.15; $[\alpha]_D^{23}$ -21.1 (*c* 1.02, $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 1700 (C=O), 1388 (CMe$_3$), 1254 (SiMe$_2$), 1078 (Si-O), 837 (SiMe$_2$); δ_H (300 MHz, $CDCl_3$) 0.10 (6H, s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 1.30 (3H, d, *J* 6.0, CH*Me*), 1.47 (9H, s, OC*Me*$_3$), 1.52, 1.68 (6H, 2xs, *Me*-oxazolidine), 3.90-4.00 (1H, br.m, C*H*Me), 4.33 (2H, d, *J* 1.5, C*H*$_2$OTBS) and 4.40 (1H, m, C*H*CHMe); δ_C (100.6 MHz, $CDCl_3$) -5.2 (CH_3, Si*Me*$_2$), 18.2 (C, SiCMe$_3$), 19.4 (brCH_3, CH*Me*), 25.7 (CH_3, SiC*Me*$_3$), 26.3, 27.5 (2xbrCH_3, *Me*-oxazolidine), 28.4 (CH_3, OC*Me*$_3$), 51.6 (CH_2, *C*H$_2$OTBS), 59.5 (CH, *C*HMe), 70.7 (CH, *C*HCHMe), 79.8 (C, OCMe$_3$), 83.1, 84.7 (2xC, *C*-acetylene), 95.3 (C, *C*-oxazolidine) and 151.6 (C, *C*=O); *m/z* (E.I.) 383 (M^+, 0.1%), 268 (73), 57 (100); (Found: M^+, 383.25050. $C_{20}H_{37}NO_4Si$ requires M, 383.24919).

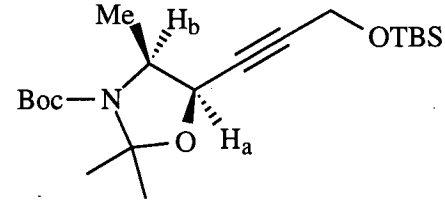
nOe data for **56**:-



Irradiated Proton	Enhancement Observed (%)
H_a	H_b (2%); Me (6%)
H_b	H_a (3%); Me (6%)
Me	H_a (10%); H_b (12%)

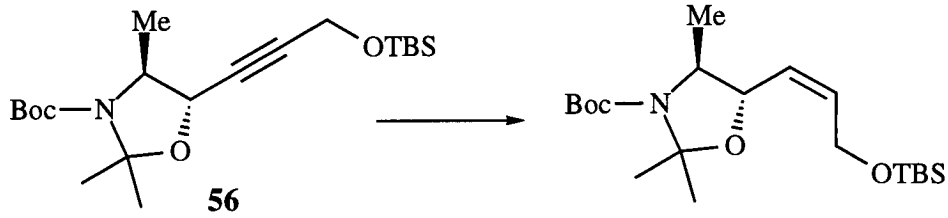
(4*S*, 5*R*)-*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[3-(*tert*-butyldimethylsilyl oxy)prop-1-yn-1-yl]oxazolidine **57**: R_F 0.13; $[\alpha]_D^{25}$ +1.05 (*c* 0.95, $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 1701 (C=O), 1384 (CMe_3), 1254 ($SiMe_2$), 1092 (Si-O), 837 ($SiMe_2$); δ_H (300 MHz, $CDCl_3$) 0.11 (6H, s, Si*Me*$_2$), 0.9 (9H, s, SiC*Me*$_3$), 1.29 (3H, m, CH*Me*), 1.46 (9H, s, OC*Me*$_3$), 1.50-1.66 (6H, br.m, 2x*Me*-oxazolidine), 3.71-4.10 (1H, br.m, C*H*Me), 4.31 (2H, d, *J* 1.5, C*H*$_2$OTBS) and 4.75 (1H, dt, *J* 5.5, 1.5, C*H*CHMe); *m/z* (E.I.) 383 (M^+, 1.1%), 368 (28), 268 (65), 57 (100); (Found: M^+, 383.24980. $C_{20}H_{37}NO_4Si$ requires M, 383.24919).

nOe data for **57**:-



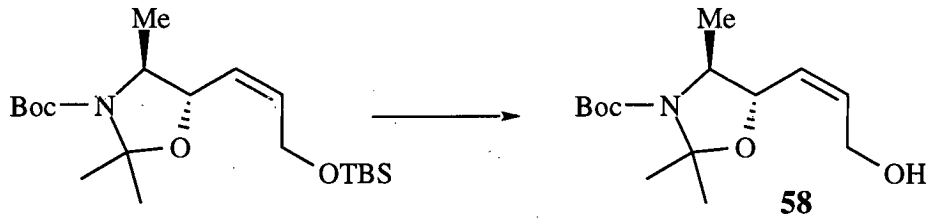
Irradiated Proton	Enhancement Observed (%)
H_a	H_b (10%)
H_b	H_a (7%); Me (2%)
Me	H_a (8%)

5.2.6 (4S, 5S)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(Z)-3-(tert-butyldimethylsilyloxy)prop-1-en--yl]oxazolidine



A stirred deoxygenated solution of the acetylene **56** (422 mg, 1.10 mmol) in hexane (10 ml) was treated with palladium on calcium carbonate (Lindlar catalyst, 30 mg) and stirred under an atmosphere of hydrogen for 20 hours. The catalyst was removed by filtration through celite, washed with ether (2 x 5 ml), and the combined filtrates concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (7:1) yielded *the Z-alkene*[68] (399 mg, 94%). R_F 0.44; δ_H (250 MHz, $CDCl_3$) 0.05 (6H, s, Si*Me*$_2$), 0.88 (9H, s, SiC*Me*$_3$), 1.26 (3H, d, *J* 6.0, CH*Me*), 1.46 (9H, s, OC*Me*$_3$), 1.49, 1.56 (6H, 2xs, *Me*-oxazolidine), 3.4-3.5 (1H, br.m, C*H*Me), 4.27-4.30 (2H, m, C*H*$_2$OSi), 4.40 (1H, m, C*H*CHMe), 5.47 (1H, ov. dddd, *J* 11.0, 8.0, 2.0, 2.0, C*H*CHCH$_2$OTBS) and 5.75 (1H, dddd, *J* 11.0, 6.0, 6.0, 1.0), C*H*CH$_2$OTBS).

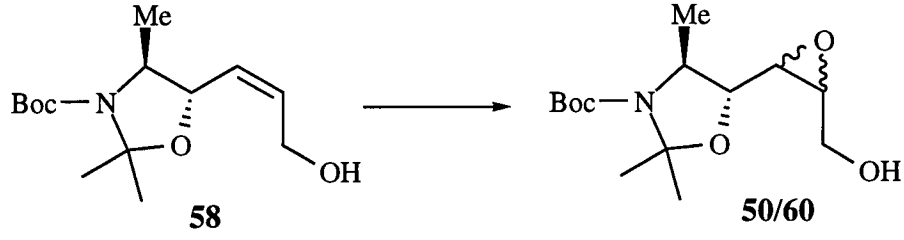
5.2.7 (4S, 5S)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(Z)-3-hydroxy prop-1-en-1-yl]oxazolidine 58



A stirred solution of the Z-alkene (255 mg, 0.66 mmol) in THF (5 ml) was treated with TBAF (1M in THF, 1 ml, 0.99 mmol) at room temperature for 1 hour. The mixture was concentrated under reduced pressure and partitioned between ether (5 ml) and water (5 ml). The layers were separated and the organic extract washed with water (20 ml), 0.5M HCl (10 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was subjected to column chromatography eluting with petrol-EtOAc (2:1) to yield the *Z-allylic alcohol*[68] **58** as a colourless oily residue (138 mg, 77%). R_F 0.22; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.0, CH*Me*), 1.46 (9H, s,

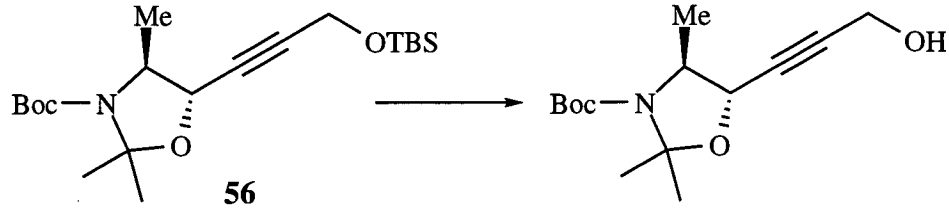
OC*Me*$_3$), 1.50, 1.57 (6H, 2xs, *Me*-oxazolidine), 2.0-2.1 (1H, br.s, O*H*), 3.50 (1H, m, C*H*Me), 1.16-1.24 (2H, m, C*H*$_2$OH), 4.40 (1H, m, C*H*CHMe), 5.47 (1H, ov. dddd, *J* 11.0, 8.5, 1.5, 1.5, C*H*CHCH$_2$OH) and 5.75 (1H, ov. dddd, *J* 11.0, 7.0, 6.0, 6.0, C*H*CH$_2$OH).

*5.2.8 (4*S, *5*R*)*-N-(tert-*butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1*RS, *2*SR*)-1,2-epoxy-3-hydroxypropan-1-yl]oxazolidine* ***59/60***



To a solution of the allylic alcohol **58** (89 mg, 0.33 mmol) in dry DCM (5 ml) was added *meta*-chloroperbenzoic acid (116 mg, 0.67 mmol) and stirring continued at room temperature for 48 hours under a nitrogen atmosphere. The reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ (10 ml), the organic phase separated and washed with sat. aq. $NaHCO_3$ (10 ml), brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The mixture was not purified by chromatography hence no yield was recorded.

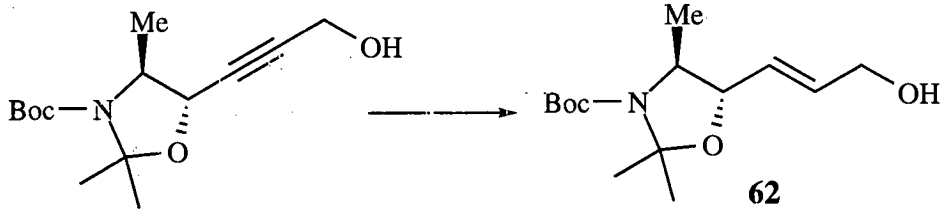
*5.2.9 (4*S, *5*S*)*-N-(tert-*butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[3-hydroxyprop-1-yn-1-yl]oxazolidine*



A stirred solution of the acetylene **56** (264 mg, 0.69 mmol) in THF (5 ml) was treated with TBAF (1M soln in THF, 0.88 ml, 0.97 mmol) at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue dissolved in ether (10 ml) and washed with water (2 x 10 ml) and 0.5M HCl (10 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography eluting with petrol-EtOAc (3:1) to yield the *propargyl alcohol* as a

colourless oil (168 mg, 90%). R_F 0.20; $[\alpha]_D^{27}$ -146.3 (*c* 0.99 in $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 3440br (OH), 1694 (C=O), 1392 (CMe_3), 1083 (C-O); δ_H (300 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.0, CH*Me*), 1.48 (9H, s, OC*Me*$_3$), 1.52, 1.68 (6H, 2xs, *Me*-oxazolidine), 1.68-1.90 (1H, br.s, O*H*), 4.00-4.10 (1H, br.m, C*H*Me), 4.30 (2H, s, C*H*$_2$OH) and 4.43 (1H, m, C*H*CHMe); δ_C (75.5 MHz, $CDCl_3$) 19.4 (CH_3, CH*Me*), 26.3, 27.3 (2xCH_3, *Me*-oxazolidine), 28.3 (CH_3, OC*Me*$_3$), 50.3 (CH_2, *C*H$_2$OH), 59.4 (CH, *C*HMe), 70.6 (CH, *C*HCHMe), 80.0 (C, O*C*Me$_3$), 82.8, 84.8 (2xC, *C*-acetylene), 95.1 (C, *C*-oxazolidine) and 151.7 (C, *C*=O); *m/z* (F.A.B.) 269 (M^+, 1.7%), 254 (74), 198 (78), 154 (77), 57 (88); (Found: M^+, 269.16378. $C_{14}H_{23}NO_4$ requires M, 269.34092).

5.2.10 (4S, 5S)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(E)-3-hydroxy prop-1-en-1-yl]oxazolidine **62**

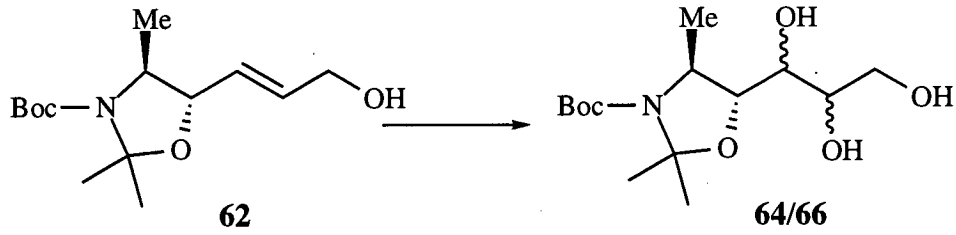


62

Lithium aluminium hydride (50 mg, 1.32 mmol) was added slowly to a stirred solution of the prepared propargyl alcohol (225 mg, 0.83 mmol) in THF (12 ml) and stirring continued under an atmosphere of nitrogen for 2 hours. The reaction was quenched by addition of EtOAc (10 ml) followed by sat. aq. NH_4Cl (10 ml) and the resulting precipitate filtered through a plug of Celite and washed with EtOAc (2 x 3 ml). The combined filtrates were separated and the organic extract washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated before subjecting the residue to column chromatography eluting with petrol-EtOAc (2:1) resulting in *the E-allylic alcohol* **62** (202 mg, 90%). R_F 0.20; $[\alpha]_D^{31}$ +26.4 (*c* 0.99 in $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 3200-3600br (OH), 1699 (C=O), 1388 (CMe_3), 1105, 1136 (C-O); δ_H (300 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.0, CH*Me*), 1.45 (9H, s, OC*Me*$_3$), 1.48, 1.56 (6H, 2xs, *Me*-oxazolidine), 2.00-2.30 (1H, br.s, O*H*), 3.52 (1H, m, C*H*Me), 4.07 (1H, dd, *J* 7.5, 7.5, C*H*CHMe), 4.15 (2H, dd, *J* 5.0, 1.5, C*H*$_2$OH), 5.73 (1H, ddt, *J* 15.5, 7.5, 1.5, C*H*CHCH$_2$OH) and 5.96 (1H, dtd, *J* 15.5, 5.0, 0.5, C*H*CH$_2$OH); δ_C (75.5 MHz, $CDCl_3$), 19.4 (CH_3, CH*Me*), 26.4, 27.0 (2xCH_3, *Me*-oxazolidine), 28.3 (CH_3, OC*Me*$_3$), 57.9 (CH, *C*HMe), 62.5 (CH_2, *C*H$_2$OH), 79.8 (C, O*C*Me$_3$), 81.9 (CH, *C*HCHMe), 95.3 (C, *C*-oxazolidine), 128.1, 134.2 (2xCH, *C*H-alkene) and 152.0

(C, *C*=O); *m/z* (E.I.) 271 (M^+, 0.1%), 256 (9), 57 (100); (Found: M^+, 271.17935. $C_{14}H_{25}NO_4$ requires M, 271.17836).

5.2.11 (4S, 5S)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1RS, 2RS)-1,2, 3 -trihydroxypropan-1-yl]oxazolidine ***64/66***



62 **64/66**

Method 1. Catalytic osmium tetroxide:-

The *E*-allylic alcohol **62** (1.50 g, 5.53 mmol) in acetone (20 ml) was added to a stirred solution of *N*-methylmorpholine-*N*-oxide (648 mg, 5.53 mmol) and osmium tetroxide (100 mg, 0.39 mmol) in acetone (10 ml) and water (10 ml) and the bi-phasic mixture stirred for 16 hours. The reaction was quenched by addition of sodium hydrosulfite (0.6 g) and fluorosil (5 g) in water (20 ml) and the slurry stirred for 20 minutes before filtration through a plug of Celite and concentration under reduced pressure. Column chromatography of the residue eluting with EtOAc gave the *triol diastereomers* **64** and **66** in a combined yield of 1.35 g (84%) as an oily residue. This combined mixture of diastereomers was then subjected to column chromatography eluting slowly with EtOAc to enable sufficient separation of the pure diastereomer triols **64** and **66**.

Method 2. Sharpless asymmetric dihydroxylation mix (AD-mix):-

To a stirred mixture of cooled (0°C) methane sulfonamide (30 mg, 0.32 mmol) and AD-mix-β (446 mg) in *t*-butanol (1.6 ml) and water (1.6 ml) was added a solution of *E*-allylic alcohol **62** (86 mg, 0.32 mmol) in *t*-butanol (0.5 ml). Stirring was continued at 0°C for 10 hours then at room temperature for a further 24 hours, whereafter magnesium sulfate (0.5 g) was added and the mixture stirred for 30 minutes then extracted with EtOAc (3 x 5 ml). The combined organic fractions were washed with 2M KOH (5 ml), brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with EtOAc gave recovered starting material **62** (40 mg) and the *triol diastereomers* **64/66** in a combined yield of 19 mg (20%).

Method 3, Catalytic ruthenium tetroxide:-

To a stirred and cooled (0-5°C) solution of *E*-allylic alcohol (35 mg, 0.13 mmol) in EtOAc/CH_3CN (1.54 ml, 1:1) was added a solution of ruthenium (III) chloride hydrate (2 mg, 7 mol%) and sodium periodate (43 mg, 1.5 eq.) in water (0.25 ml). The resulting biphasic mixture was stirred vigorously for 3 minutes and then quenched with sat. aq. $Na_2S_2O_3$ (0.77 ml) and the aqueous liqours extracted with EtOAc (2 x 5 ml), dried over anhydrous Na_2SO_4, and concentrated. Column chromatography of the residue (EtOAc) gave recovered starting material **62** (15 mg) and the *triol diastereomers* **64/66** (12 mg, 30%).

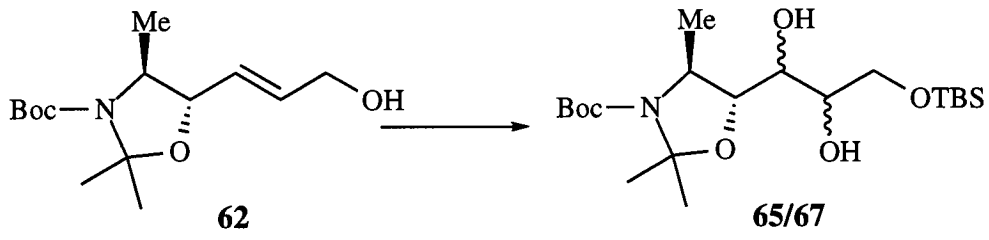
N.B. Ratio determination of the triol diastereomers was obtained by comparison of the integrals of the oxazolidine methyl doublets in the ^1H nmr spectrum which was recorded on the combined diastereomer mixture.

(4*S*, 5*R*)-*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2R)-1,2,3-trihydro xypropan-1-yl]oxazolidine **64**:- mp 40-45°C; R_F (EtOAc) 0.30; $[\alpha]_D^{23}$ +8.79 (*c* 1.01 in $CHCl_3$); υ_{max}/cm^{-1} (KBr disc) 3600-3200br (OH), 1700 (C=O), 1392 (CMe_3), 1099 (C-O); δ_H (400 MHz, CD_3OD) 1.36 (3H, d, *J* 6.0, CH*Me*), 1.48 (9H, s, O*CMe*$_3$), 1.50, 1.54 (6H, 2xs, *Me*-oxazolidine), 3.55 (1H, dd, *J* 9.0, 1.5, C*H*CHCH$_2$), 3.60 (2H, m, C*H*$_2$OH), 3.84 (1H, dd, *J* 9.0, 4.0, C*H*CHMe), 3.85 (1H, m, C*H*CH$_2$) and 4.01-4.05 (1H, br.m, C*H*Me); δ_C (100.6 MHz, CD_3OD), 19.5 (CH_3, CH*Me*), 26.1, 26.8 (2xCH_3, *Me*-oxazolidine), 27.4 (CH_3, O*CMe*$_3$), 56.3 (brCH, *C*HMe), 62.9 (CH_2, *C*H$_2$OH), 69.9 (CH, *C*HCH$_2$), 71.4 (CH, *C*HCHCH$_2$), 80.7 (brC, O*C*Me$_3$), 81.1 (brCH, *C*HCHMe), 94.1 (brC, *C*-oxazolidine) and 152.2 (C, *C*=O); *m/z* (F.A.B.) 306 [(MH)$^+$, 54.4%], 290 (17), 109 (9); [Found: (MH)$^+$, 306.19266. $C_{14}H_{28}NO_6$ requires MH, 306.19166].

(4*S*, 5*R*)-*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1S, 2S)-1,2,3-trihydro xypropan-1-yl]oxazolidine **66**:- R_F (EtOAc) 0.25; δ_H (200 MHz, $CDCl_3$) 1.32 (3H, m, CH*Me*), 1.45 (9H, s, O*CMe*$_3$), 1.49, 1.52 (6H, 2xs, *Me*-oxazolidine), 3.0-3.1 (2H, br.s, 2xO*H*), 3.2-3.4 (1H, br.s, O*H*), 3.62 (1H, br.m, C*H*), 3.74 (3H, br.m, C*H*$_2$OH and CH) and 3.86 (2H, br.m, 2xC*H*); δ_C (50.1 MHz, $CDCl_3$) 19.0 (CH_3, CH*Me*), 25.4 (CH_3, 2x*Me*-oxazolidine), 27.0 (CH_3, O*CMe*$_3$), 52.7 (CH, *C*HMe), 62.6 (CH_2, *C*H$_2$OH), 69.2 (CH, *C*HCH$_2$), 70.8 (CH, *C*HCHCH$_2$), 78.8 (C, O*C*Me$_3$), 80.8 (CH, *C*HCHMe), 93.4 (C, *C*Me$_2$) and 150.7 (C, *C*=O).

5.2.12 (4S, 5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1RS, 2RS)-3-(tert-butyldimethylsilyloxy)-1,2-dihydroxypropan-1-yl]oxazolidine ***65/67***

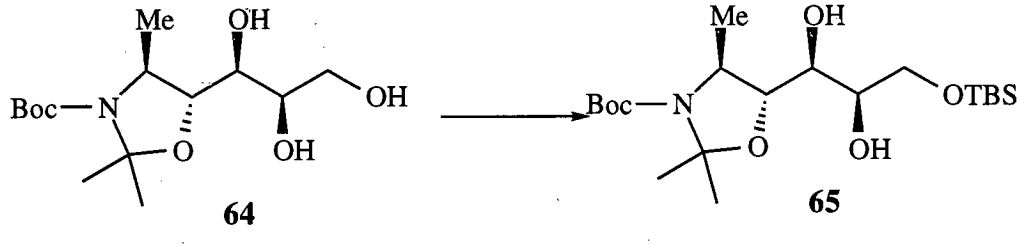
Method 1, From the E*-allylic alcohol* ***62****:-*



62 **65/67**

A stirred solution of *E*-allylic alcohol **62** (107 mg, 0.40 mmol) in DMF (5 ml) was treated with *tert*-butyldimethylsilyl chloride (72 mg, 0.47 mmol) and imidazole (69 mg, 0.99 mmol) under a nitrogen atmosphere. Stirring was continued for 1 hour whereafter the reaction was quenched by addition of water (5 ml) and extracted with EtOAc (2 x 5 ml). The combined organic extracts were washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-EtOAc (4:1) gave the *TBS ether* **63** (138 mg, 90%). To a stirred solution of potassium hexaferricyanide (445 mg, 1.35 mmol), potassium bicarbonate (191 mg, 1.38 mmol) and potassium osmate (VI) dihydrate (5 mg, 0.013 mmol) in water (2.5 ml) was added the TBS ether **63** (58 mg, 0.15 mmol) as a solution in *t*-butanol (2.5 ml). The resulting bi-phasic mixture was stirred at room temperature for 17 hours whereafter Na_2SO_3 (350 mg) was added and the mixture stirred for a further 20 minutes before separation of the layers. Extraction of the aqueous layer with chloroform (2 x 5 ml) was followed by drying of the combined organic extracts over anhydrous Na_2SO_4 and concentration *in vacuo*. Column chromatography eluting with petrol-EtOAc (5:1) gave the *diol diastereomers* **65/67** in a combined yield 37 mg (77%), and a ratio of 3:1 (as determined by nmr analysis).

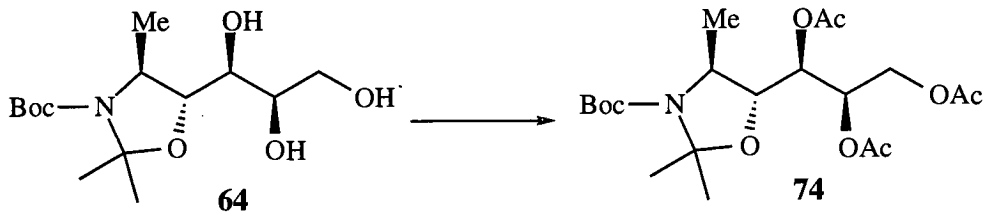
Method 2, From the triol ***64****:-*



64 **65**

To a cooled (-10°C) stirred solution of the triol **64** (245 mg, 0.80 mmol) in DCM (10 ml) was added 2,6-lutidine (215 µl, 0.18 mmol) and *tert*-butyldimethylsilyl triflate (2.03 µl, 0.88 mmol) under an atmosphere of nitrogen. The mixture was stirred for 2 hours at that temperature and then at room temperature for 1 hour. The reaction was quenched by addition of EtOAc (10 ml) and water (10 ml) and the organic layer washed with 0.3M $KHSO_4$ (20 ml), water (10 ml) and brine (10 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated and the residue subjected to column chromatography eluting with petrol-EtOAc (3:1) to yield the single diastereomer (4*S*, 5*R*)-*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(*1*R, 2R)-3-(*tert*-butyldimethylsilyloxy)-1,2-dihydroxypropan-1-yl]oxazolidine **65** (252 mg, 75%) as an oily residue. R_F (petrol-EtOAc 1:1) 0.75; $[\alpha]_D^{26}$ +8.75 (*c* 0.98 in $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 3200-3600br (OH), 1704 (C=O), 1387 (CMe_3), 1261 ($SiMe_2$), 1109 (Si-O), 851 ($SiMe_2$); δ_H (400 MHz, $CDCl_3$), 0.06 (6H, s, Si*Me*$_2$), 0.88 (9H, s, SiC*Me*$_3$), 1.34 (3H, d, *J* 6.0, CH*Me*), 1.44 (9H, s, OC*Me*$_3$), 1.48, 1.51 (6H, 2xs, *Me*-oxazolidine), 2.79 (1H, br.m, O*H*), 3.01 (1H, br.m, O*H*), 3.58 (1H, m, C*H*CHCH$_2$), 3.68-3.70 (3H, m, C*H*$_2$OH and C*H*CHMe), 3.86 (1H, m, C*H*CH$_2$) and 3.86-3.97 (1H, br.m, C*H*Me); δ_C (100.6 MHz, $CDCl_3$) -5.5 (CH_3, Si*Me*$_2$), 18.2 (C, OSi*C*Me$_3$), 20.7 (CH_3, CH*Me*), 25.8 (CH_3, OSiC*Me*$_3$), 27.0, 27.7 (2xCH_3, *Me*-oxazolidine), 28.5 (CH_3, OC*Me*$_3$), 55.9 (CH, *C*HMe), 65.9 (CH_2, *C*H$_2$OTBS), 69.1 (CH, *C*HCH$_2$), 72.8 (CH, *C*HCHCH$_2$), 79.6 (C, O*C*Me$_3$), 81.5 (CH, *C*HCHMe), 94.5 (C, *C*-oxazolidine) and 151.8 (C, *C*=O); *m/z* (F.A.B.) 420 [(MH)$^+$, 81.9%], 404 (13), 304 (73), 115 (42), 57 (39); [Found: (MH)$^+$, 420.27787. $C_{20}H_{42}NO_6Si$ requires MH, 420.27829].

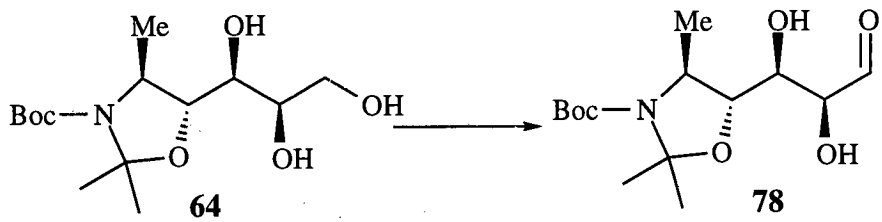
*5.2.13 (4*S, *5*R*)-*N*-(tert-*butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2R)-1,2,3-triacetoxypropan-1-yl]oxazolidine **74***



A solution of the triol **64** (38 mg, 0.12 mmol) in acetic anhydride (1 ml) and pyridine (1 ml) was stirred for 1 hour whereafter dilute HCl (2 ml) was added and the product extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting oily residue was subjected to column chromatography eluting with petrol-EtOAc (1:1) to give the *acetylated triol* **74** (45 mg, 83%) as an oil. $[\alpha]_D^{27}$

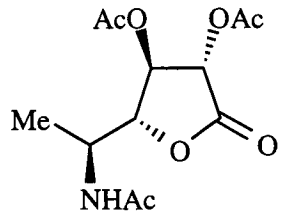
+21.23 (c 0.80, $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 1750 (C=O, acetate), 1694 (C=O, urethane), 1388 (CMe_3), 1212, 1030 (C-O); δ_H (250 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.0, CH*Me*), 1.44 (9H, s, $OCMe_3$), 1.45, 1.54 (6H, 2xs, *Me*-oxazolidine), 2.01, 2.09, 2.10 (9H, 3xs, *Me*CO), 3.7-3.8 (1H, br.m, C*H*Me), 3.80 (1H, dd, *J* 8.0, 4.0, C*H*CHMe), 3.96 (1H, dd, *J* 11.5, 6.5, CH_2OAc), 4.24 (1H, dd, *J* 11.5, 5.5, CH_2OAc), 5.17 (1H, dd, *J* 8.0, 3.0, C*H*$CHCH_2$) and 5.41 (1H, dq, *J* 6.5, 5.5, 3.0, C*H*CH_2); δ_C (62.9 MHz, $CDCl_3$) 19.5 (CH_3, CH*Me*), 20.5 (CH_3, CO*Me*), 27.0, 27.2 (2xCH_3, *Me*-oxazolidine), 29.5 (CH_3, $OCMe_3$), 55.4 (CH, *C*HMe), 61.7 (CH_2, *C*H_2OAc), 68.6 (CH, *C*HCH_2), 71.7 (CH, *C*H$CHCH_2$), 78.8 (CH, *C*HCHMe), 79.3 (C, O*C*Me_3), 94.3 (C, *C*-oxazolidine), 151.4 (C, *C*=O urethane) and 169.6, 169.7, 170.3 (3xC, *C*=O acetate); *m/z* (F.A.B.) 432 [$(MH)^+$, 35.6%), 416 (44), 372 (14), 57 (69); [Found: $(MH)^+$, 432.22340. $C_{20}H_{34}NO_9$ requires MH, 432.22334].

*5.2.14 (4S, 5R)-N-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2S)-1,2-di hydroxy-3-oxo-propan-1-yl]oxazolidine 78*



A solution of NaBr (4 mg, 12 mol %) and BTAC (4 mg, 5 mol%) in sat. aq. $NaHCO_3$ (0.5 ml) was added to a vigorously stirred solution of the triol **64** (101 mg, 0.33 mmol) and TEMPO (2 mg, 3 mol%) in DCM (2 ml). The resulting bi-phasic mixture was cooled to 0°C, and a solution of sodium hypochlorite (1.12M, 0.70 ml), sat. aq. $NaHCO_3$ (0.6 ml) and brine (1.2 ml) was added dropwise over 40 minutes. The mixture was allowed to stir for 30 minutes at 0°C, then at 20°C for a further 20 minutes. The phases were separated and the aqueous layer extracted with DCM (2 x 10ml). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 ml), brine (10 ml), dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to yield a white solid (100 mg) which was used in the next step without further purification.

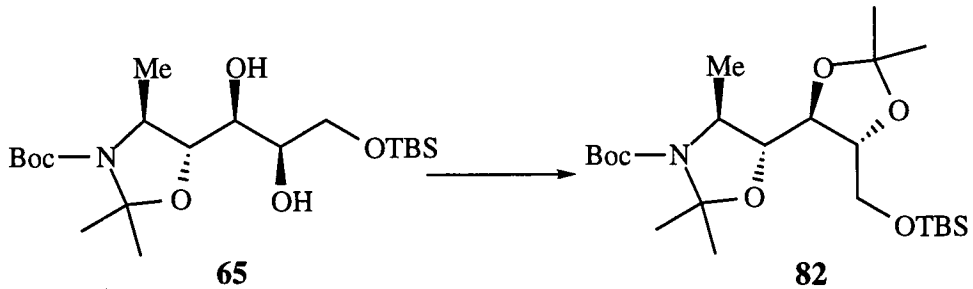
5.2.15 Nitrogen deprotection and ring closure to yield (2S, 3R, 4R, 5S)-2,3-diacet oxy-5-acetamido-γ-hexanolactone ***80***



80

The crude residue from the previous reaction was treated with 90% aq. trifluoroacetic acid (5 ml) and the mixture was stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the residue dissolved in water (0.5 ml), and passed through a column of Amberlyst A26 basic ion exchange resin (OH^-) eluting with water. The eluant was removed *in vacuo* to produce an oily residue which was taken up in pyridine (5 ml) and treated with acetic anhydride (240 µl, 4.7 eq.) and DMAP (several crystals). The reaction was stirred at room temperature for 26 hours whereafter dilute HCl (5 ml) was added and the product extracted with EtOAc (2 x 10 ml). The combined extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography eluting with DCM-ether (1:1), then freeze dried to yield the *lactone* **80** (6 mg). υ_{max}/cm^{-1} ($CHCl_3$) 1800 (C=O lactone), 1752 (C=O acetate), 1214 (C-O); δ_H (250 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.0, CH*Me*), 2.00, 2.10, 2.16 (9H, 3xs, 3xCO*Me*), 4.38 (1H, dd, *J* 7.0, 2.0, C*H*CHNHAc), 4.48 (1H, m, C*H*NHAc), 5.29-5.44 (2H, m, C*HCH*COO), 5.66 (1H, br.d, *J* 8.0, N*H*Ac); δ_C (62.9 MHz, $CDCl_3$) 17.8 (CH_3, CH*Me*), 20.5, 23.2, 29.6 (3xCH_3, CO*Me*), 44.1 (CH, *C*HMe), 72.6, 73.3, 81.2 (3xCH, *CHCHCH*CHMe), 168.7, 169.9, 169.7, 170.2 (4xC, 3x*C*=O acetate and *C*=O lactone); *m/z* (E.I.) 288 [$(MH)^+$, 1.6%], 272 (2); [Found (C.I.): $(MH)^+$, 288.10832. $C_{12}H_{18}NO_7$ requires MH, 288.10830].

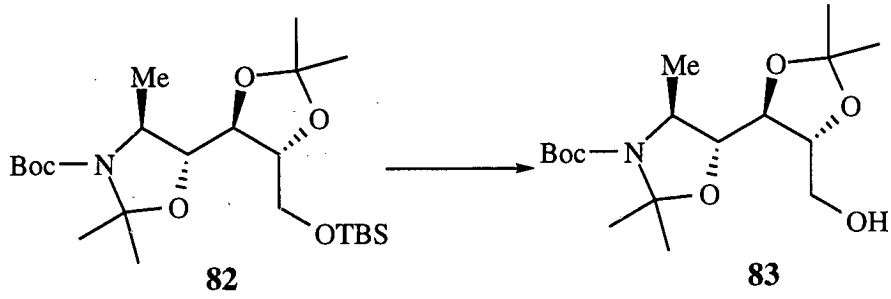
5.2.16 (4S, 5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2R)-3-(tert-butyldimethylsilyloxy)-1-2-isopropylidenepropan-1-yl]oxazolidine 82



65 **82**

A stirred solution of the diol **65** (220 mg, 0.53 mmol) in acetone (3 ml) under nitrogen was treated with 2,2-dimethoxypropane (2 ml) and boron trifluoride etherate (18 µl) at room temperature for 20 minutes. The reaction mixture was concentrated under reduced pressure and the residue taken up in DCM (10 ml) and washed with sat. aq. $NaHCO_3$ (10 ml), water (10 ml) and brine (10 ml). The organic extract was dried over anhydrous Na_2SO_4, concentrated and subjected to column chromatography eluting with petrol-ether (12:1) to yield the *acetal* **82** (206 mg, 85%) as an oil. R_F (petrol-EtOAc 8:1) 0.71; $[\alpha]_D^{24}$ +13.74 (*c* 1.01 in $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 1710 (C=O), 1390 (CMe_3), 1260 ($SiMe_2$), 1065 (Si-O), 851 ($SiMe_2$); δ_H (400 MHz, $CDCl_3$) 0.48, 0.56 (6H, 2xs, Si*Me*$_2$), 0.88 (9H, s, SiC*Me*$_3$), 1.34 (3H, d, *J* 6.0, CH*Me*), 1.37, 1.38 (6H, 2xs, *Me*-acetal), 1.46 (9H, s, OC*Me*$_3$), 1.47, 1.53 (6H, 2xs, *Me*-oxazolidine) and 3.68-3.96 (6H, m, 4xC*H* and C*H*$_2$OTBS); δ_C (100.6 MHz, $CDCl_3$) -5.3, -5.4 (2xCH_3, Si*Me*$_2$), 18.4 (C, Si*C*Me$_3$), 20.5 (CH_3, CH*Me*), 25.9 (CH_3, SiC*Me*$_3$), 27.2, 27.2 (2xCH_3, *Me*-acetal), 27.6 (brCH_3, 2x*Me*-oxazolidine), 28.5 (CH_3, OC*Me*$_3$), 56.3 (CH, *C*HMe), 63.4 (CH_2, *C*H$_2$OTBS), 77.7 (CH, *C*HCH$_2$), 79.7 (C, O*C*Me$_3$), 81.0 (CH, *C*HCHCH$_2$), 83.3 (CH, *C*HCHMe), 94.8 (C, *C*-oxazolidine), 109.5 (C, *C*-acetal) and 151.8 (C, *C*=O); *m/z* (E.I.) 459 [$(MH)^+$, 0.1%], 444 (7), 344 (37), 328 (4), 244 (20), 114 (36), 57 (100); (Found: M^+, 459.29988. $C_{23}H_{24}NO_6Si$ requires M, 459.30162).

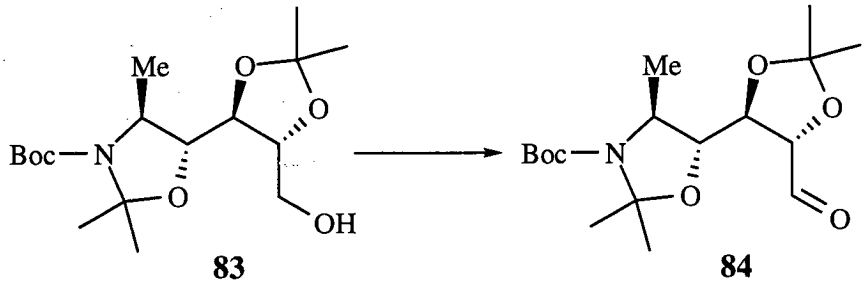
5.2.17 (4S, 5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2R)-3-hydroxy-1-2-isopropylidenepropan-1-yl]oxazolidine ***83***



82 **83**

A stirred solution of the TBS-ether **82** (212 mg, 0.46 mmol) in THF (8 ml) was treated with TBAF (1M in THF, 0.9 ml, 0.92 mmol) at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue partitioned between ether and water (10 ml). The organic layer was washed with 0.5M HCl (10 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with petrol-EtOAc (2:1) yielded the *primary alcohol* **83** (127 mg, 80%). R_F (petrol-EtOAc 5:1) 0.68; $[\alpha]_D^{22}$ +19.9 (*c* 1.05 in $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 3200-3700br (OH), 1695 (C=O), 1368 (CMe_3), 1091 (C-O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.0, CH*Me*), 1.36, 1.38 (6H, 2xs, *Me*-acetal), 1.45 (9H, s, OCMe_3), 1.47, 1.53 (6H, 2xs, *Me*-oxazolidine), 2.25-2.40 (1H, br.s, O*H*) and 3.67-3.99 (6H, m, 4xC*H* and CH_2); δ_C (100.6 MHz, $CDCl_3$) 19.2-20.5 (brCH_3, CH*Me*), 26.5, 26.9 (2xCH_3, *Me*-acetal), 27.0-28.4 (2xbrCH_3, *Me*-oxazolidine), 28.4 (CH_3, OCMe_3), 56.9 (brCH, *C*HMe), 62.6 (CH_2, *C*H_2OH), 78.5 (CH, *C*HCH_2), 79.9 (C, OCMe_3), 81.0 (CH, *C*HCHCH_2), 83.0 (CH, *C*HCHMe), 94.9 (C, *C*-oxazolidine), 109.5 (C, *C*-acetal) and 151.7 (C, *C*=O); *m/z* (E.I.) 345 (M^+, 0.1%), 330 (20), 230 (45), 214 (10), 57 (100); (Found: M^+, 345.21478. $C_{17}H_{31}NO_6$ requires M, 345.21514).

5.2.18 (4S, 5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2S)-1-2-isopropylidene-3-oxo-propan-1-yl]oxazolidine ***84***



83 **84**

Method 1, TPAP Oxidation:-

A solution of the alcohol **83** (42 mg, 0.12 mmol) in DCM (4 ml) was stirred with crushed 3Å molecular sieves under a nitrogen atmosphere for 10 minutes. *N*-Methyl-*N*-morpholine-*N*-oxide (24 mg, 0.18 mmol) was added followed by tetrapropyl ammonium perruthenate, TPAP (3 mg, 5 mol%) and the mixture stirred at room temperature for 28 hours. Concentration of the solution under reduced pressure and column chromatography of the residue eluting with petrol-EtOAc (5:1) gave a product **84** as an oily residue at R_F 0.45 (6 mg) along with recovered starting material **83** (10 mg), both were complex by nmr analysis.

Method 2, Swern Oxidation:-

A solution of dimethyl sulfoxide (21 µl, 0.30 mmol) in DCM (2 ml) was added dropwise to a cooled (-70°C) stirred solution of oxalyl chloride (71 µl, 0.14 mmol) in DCM (6 ml) under a nitrogen atmosphere. The resulting mixture was stirred at -50°C for 10 minutes and then cooled to -70°C and a solution of the alcohol **83** (44 mg, 0.13 mmol) in DCM (2 ml) added dropwise whilst maintaining the temperature below -65°C. The solution was stirred for 30 minutes at this temperature before dropwise addition of triethylamine (52 µl, 0.38 mmol), and then stirred for a further 30 minutes at -50°C. DCM (10 ml) was added and the reaction warmed to 0°C where water (5ml) was added and the organic phase washed with 0.1M HCl (10 ml), brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography eluting with petrol-EtOAc (2:1) yielded starting material **83** (36 mg).

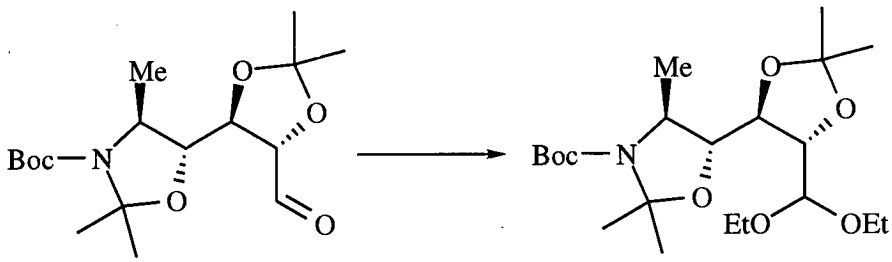
Method 3, IBX oxidation:-

A stirred solution of *o*-iodoxybenzoic acid, IBX (45 mg, 0.16 mmol) in DMSO (2 ml) was stirred for 10 minutes at room temperature before addition of the alcohol **83** (50 mg, 0.15 mmol) as a solution in DMSO (1 ml). Stirring was continued for 48 hours then the reaction was quenched by the addition of water (5 ml). The mixture was filtered through a plug of Celite and the filtrates extracted with EtOAc (2 x 10 ml). The organic fraction was washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated to give a residue (41%) which was observed to be a streaky mixture when visualised by tlc.

Method 4. TEMPO oxidation:-

A solution of NaBr (7 mg, 12 mol%) and BTAC (5 mg, 5 mol%) in sat. aq. $NaHCO_3$ (0.8 ml) was added to a vigorously stirred solution of the diol **83** (179 mg, 0.52 mmol) and TEMPO (2 mg, 2.5 mol%) in DCM (2 ml). The bi-phasic mixture was cooled to 0°C and a solution of sodium hypochlorite (0.6 ml, 30% excess), sat. aq. $NaHCO_3$ (0.5 ml) and brine (1.0 ml) added dropwise over 20 minutes. The mixture was allowed to stir for 30 minutes at 0°C, then at room temperature for a further 15 minutes. The aqueous layer was extracted with DCM (2 x 5 ml) and the combined organic fractions washed with sat. aq. $NaHCO_3$ (5 ml), brine (5 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* gave the crude *aldehyde* **84** (165 mg, 93%) as an oil. υ_{max}/cm^{-1} ($CHCl_3$) 1736 (C=O, aldehyde), 1689 (C=O, urethane), 1375 (CMe_2), 1075 (C-O); δ_C (62.9 MHz, $CDCl_3$) 20.0 (brCH_3, CH*Me*), 26.2-28.3 (4xCH_3, 2x*Me*-oxazolidine, 2x*Me*-acetal), 29.5 (CH_3, OC*Me*$_3$), 55.9 (CH, *C*HMe), 77.7 (C, *C*HCHO), 79.8 (C, O*C*Me$_3$), 82.2, 83.1 (2xCH, *CH*CHCHCHO), 95.6 (C, *C*-oxazolidine), 111.5 (C, *C*-acetal), 151.5 (C, *C*=O) and 199.8 (CH, *C*=O aldehyde); *m/z* (F.A.B.) 344 [$(MH)^+$, 10.6%], 244 (82), 57 (63); [Found: $(MH)^+$, 344.20464. $C_{17}H_{30}NO_6$ requires MH, 344.20731]. N.B The ^1H nmr spectrum was complex and difficult to assign.

*5.2.19 (4S, 5R)-N-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2S)-3-di ethylacetal-1-2-*iso*propylidenepropan-1-yl]oxazolidine* ***85***



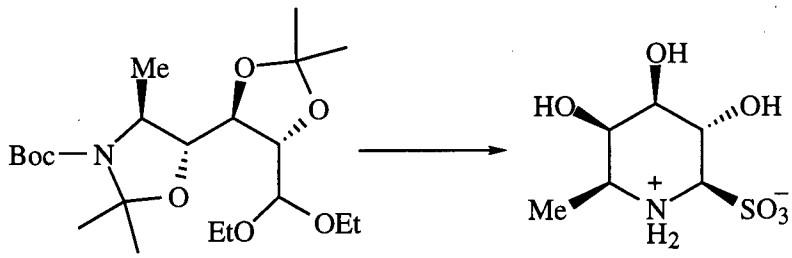
84 **85**

A stirred solution of the aldehyde **84** (37 mg, 0.11 mmol) in ethanol (1.5 ml) over activated 4Å molecular sieves was treated with triethyl orthoformate (0.5 ml) under an argon atmosphere. *para*-Toluenesulfonic acid (several crystals) was added and the solution stirred for 18 hours before addition of triethylamine (2 drops) to neutralise the solution. The sieves were removed by filtration and the solvent removed under reduced pressure. Column chromatography eluting with DCM gave the *diethyl acetal* **85** (18

mg, 40%) as an oil. R_F 0.28; υ_{max}/cm^{-1} (film, NaCl) 1700 (C=O), 1372 (CMe_2), 1087 (C-O); δ_H (360 MHz, $CDCl_3$), 1.18-1.28 (6H, ov.t, *J* 7.0, 2xOCH_2*Me*), 1.32 (3H, d, *J* 6.0, CH*Me*), 1.45 (9H, s, $OCMe_3$), 1.46-1.65 (12H, 4xs, 2x*Me*-oxazolidine and 2x*Me*-acetal), 3.58 (2H, dq, *J* 7.0, 2.0, OCH_2Me), 3.75 (2H, dq, *J* 7.0, 2.0, OCH_2Me), 3.85 (1H, t, *J* 5.0, *CH*CHMe), 3.99 (1H, dd, *J* 6.0, 5.0, *CH*$CHOEt_2$), 3.90-4.00 (1H, br.m, *CH*Me), 4.09 (1H, ov.dd, *J* 6.0, 5.0, *CH*CHCHOEt_2) and 4.49 (1H, d, *J* 5.0, *CH*OEt_2); δ_C (62.9 MHz, $CDCl_3$) 15.0, 15.1 (2xCH_3, 2xOCH_2*Me*), 20.4 (CH_3, CH*Me*), 27.0-27.6 (brCH_3, 2x*Me*-oxazolidine and 2x*Me*-acetal), 28.3 (CH_3, $OCMe_3$), 54.4 (CH, *C*HMe), 62.9, 63.8 (2xCH_2, 2xOCH_2Me), 78.5, 78.9 (2xCH, *CH*CHCHOEt_2), 79.4 (C, *C*OMe_3), 82.2 (CH, *C*HCHMe), 94.5 (C, *C*-oxazolidine), 102.3 (CH, *C*$HOEt_2$), 110.4 (C, *C*-acetal) and 151.6 (C, *C*=O); *m/z* (F.A.B.) 418 [$(MH)^+$, 68.4%], 402 (28), 372 (19), 360 (3), 29 (100); [Found: $(MH)^+$, 418.28048. $C_{21}H_{40}NO_7$ requires MH, 418.28194].

5.2.20 (-)-1-deoxyfuconojirimycin-1-sulfonic acid 87

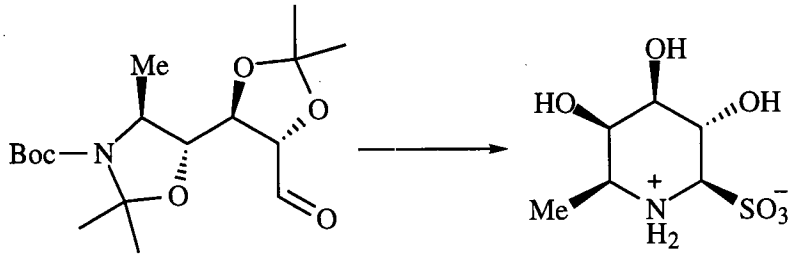
Method 1.



85 **87**

An ice cold suspension of the acetal **85** (45 mg, 0.11 mmol) in water (2.5 ml) was saturated with SO_2 gas and then stirred for 2 days at 40°C. Methanol (1ml) was added and the solution cooled to 0°C and saturated once again with SO_2. This solution was allowed to stand at this temperature for 15 hours, however no precipitate resulted. Removal of the solvent under reduced pressure yielded a white solid which was then redissolved in water (1 ml) and methanol (1 ml) and again saturated with SO_2 at 0°C. After 12 hours a white precipitate was collected by filtration and identified as the bisulphite adduct **87** (6mg, 25%).

Method 2.

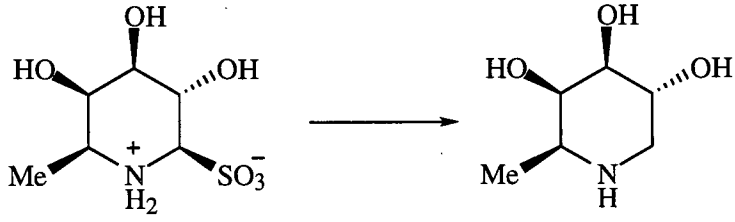


84 **87**

An ice cold suspension of the aldehyde **84** (165 mg, 0.48 mmol) in water (2 ml) was saturated with SO_2 gas and then stirred at 40°C for 48 hours. The resulting suspension was filtered to collect the precipitate and the mother liquors treated with methanol (1 ml), cooled to 0°C and saturated once more with SO_2. The resulting mixture was allowed to stand at this temperature for 8 hours and then filtered to collect the solid. The combined solid were washed with methanol (2 x 3ml) and dried to yield the *bisulfite adduct* **87** as a white solid (72 mg, 66%).

υ_{max}/cm^{-1} (KBr disc) 3353br (OH), 2489br (NH), 1157 (SO_2), 1046 (S=O); δ_H (600 MHz, D_2O) 1.22 (3H, d, *J* 6.5, CH*Me*), 3.57 (1H, dq, *J* 6.5, 1.0, C*H*Me), 3.75 (1H, dd, *J* 9.0, 3.0, C*H*CHCHMe), 4.01 (1H, dd, *J* 3.0, 1.0, C*H*CHMe), 4.09 (1H, d, *J* 10.5, C*H*SO_3) and 4.18 (1H, dd, *J* 10.5, 9.0, C*H*CHSO_3); δ_C (62.9 MHz, D_2O) 13.8 (CH_3, CH*Me*), 55.7, 66.7, 69.4, 70.3 and 72.7 (5xCH); *m/z* (F.A.B.) 228 [$(MH)^+$, 14.5%], 146 (100), 129 (17); [Found: $(MH)^+$, 228.05360. $C_6H_{13}NO_6S$ requires MH, 228.05419].

5.2.21 L-deoxyfuconojirimycin 7 (1,5-dideoxy-1,5-imino-L-fucitol)

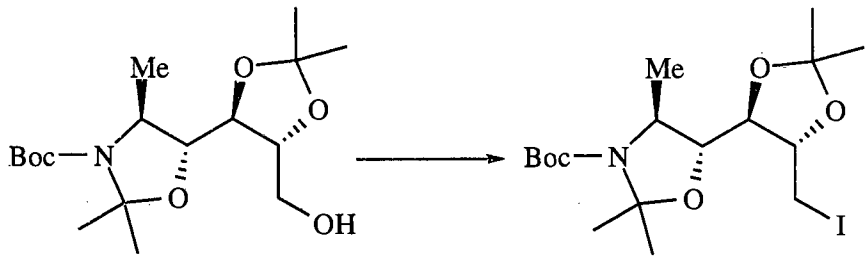


87 **7**

To a stirred suspension of the bisulphite adduct **87** (40 mg, 0.17 mmol) in water (3 ml) was added $Ba(OH)_2.8H_2O$ (55 mg, 0.18 mmol) and the resultant mixture stirred at room temperature for 1 hour. The precipitate was filtered through a plug of Celite,

washed with water (1 ml) and the combined filtrates treated with palladium (5% on charcoal, 5 mg) and the deoxygenated suspension stirred under an atmosphere of hydrogen for 15 hours. The mixture was filtered through a plug of Celite to remove the catalyst, concentrated *in vacuo* and then passed down a cation exchange resin (strong acid, Na) eluting with a gradient of 1M NH_4OH. The appropriate fractions were collected and freeze dried to give *L-deoxyfuconojirimycin*[26] **7** (22 mg, 86%). $[\alpha]_D^{21}$ -48.3 (c 0.46, H_2O); δ_H (250 MHz, D_2O) 1.06 (3H, d, *J* 7.0, CH*Me*), 2.35 (1H, dd, *J* 13.0, 11.0, C*H*$_2$NH), 2.80 (1H, dq, *J* 7.0, 1.0, C*H*Me), 3.06 (1H, dd, *J* 13.0, 5.5, C*H*$_2$NH), 3.45 (1H, dd, *J* 10.0, 3.0, C*H*CHCH$_2$), 3.67 (1H, m, C*H*CH$_2$) and 3.77 (1H, dd, *J* 3.0, 1.0, C*H*CHMe); δ_C (62.9 MHz, D_2O) 15.9 (CH_3, CH*Me*), 18.4 (CH_2, *C*H$_2$NH), 53.2 (CH, *C*HNH), 67.3, 72.2 and 74.7 (3xCH, *C*HOH).

5.2.22 (4S, 5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1R, 2S)-3-iodo-1-2-isopropylidenepropan-1-yl]oxazolidine 88



83 **88**

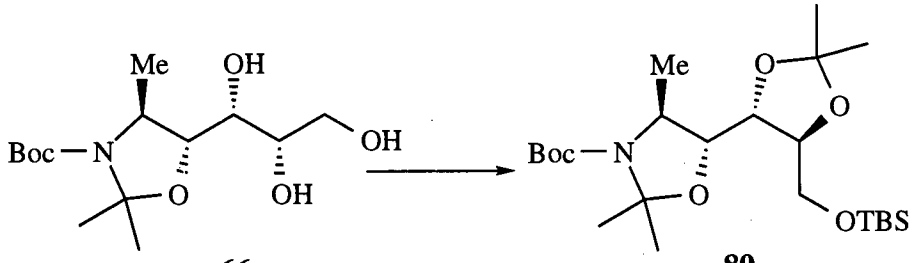
Iodine (41 mg, 0.16 mmol) was added in portions to a stirred solution of the primary alcohol **83** (38 mg, 0.11 mmol), imidazole (12 mg, 0.17 mmol), and triphenyl phosphine (42 mg, 0.16 mmol) in ether/acetonitrile (3:1, 4 ml) and the mixture stirred at room temperature for 22 hours. The precipitate was filtered through a plug of Celite, washed with ether (2 x 5 ml) and the combined filtrates concentrated under reduced pressure. The oily residue was subjected to column chromatography eluting with petrol-EtOAc (5:1) to yield the *iodo compound* **88** (23 mg, 45%) as a white solid and recovered starting material **83** (13 mg). R_F 0.85; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.0, CH*Me*), 1.39, 1.47 (6H, 2xs, *Me*-acetal), 1.47 (9H, s, OC*Me*$_3$), 1.49, 1.57 (6H, 2xs, *Me*-oxazolidine), 3.32 (1H, dd, *J* 10.5, 5.5, C*H*$_2$I), 3.53 (1H, d.d, *J* 10.5, 3.5, C*H*$_2$I), 3.67-3.74 (2H, m, C*H*CHCH$_2$ and C*H*CHMe) 3.80-3.84 (1H, m, C*H*CH$_2$) and 3.90-4.00 (1H, br.m, C*H*Me); δ_C (100.6 MHz, $CDCl_3$) 7.8 (CH_2, *C*H$_2$I), 19.2 (brCH$_3$, CH*Me*), 27.4, 27.5 (4xbrCH$_3$, *Me*-acetal and *Me*-oxazolidine), 28.5 (CH_3, OC*Me*$_3$), 56.8 (CH, *C*HMe), 79.0 (CH, *C*HCH$_2$), 79.9 (C, O*C*Me$_3$),

81.5 (CH, *C*HCHCH$_2$), 83.1 (CH, *C*HCHMe), 94.9 (C, *C*-oxazolidine), 109.9 (C, *C*-acetal) and 151.7 (C, *C*=O); *m/z* (E.I.) 440 [(M-15)$^+$, 19.8%], 384 (25), 340 (20), 57 (100). (Found; M$^+$, 455.11841. $C_{17}H_{30}NO_5I$ requires M, 455.11841).

*5.2.23 Attempted deprotection of (4*S*, 5*R*)-*N*-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1*R*, 2*S*)-3'-iodo-1-2-isopropylidenepropan-1-yl]oxazolidine and ring closure*

The iodo compound **88** (20 mg, 0.04 mmol) was dissolved in THF (3 ml) and 50% aq. trifluoroacetic acid (1 ml) added and stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and co-evaporated with $CHCl_3$ to remove traces of trifluoroacetic acid, but a complex mixture was observed by tlc and no purification was attempted.

*5.2.24 (4*S*, 5*R*)-*N*-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1*S*, 2*S*)-3-(tert-butyldimethylsilyloxy)-1-2-isopropylidenepropan-1-yl]oxazolidine **89***

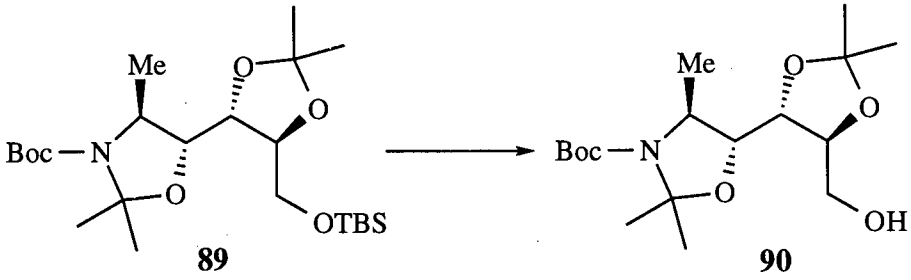


A stirred solution of the triol **66** (160 mg, 0.53 mmol) in DCM (10 ml) under an atmosphere of argon was treated with 2,6-lutidine (140 µl, 1.2 mmol) and cooled to -10°C. *tert*-Butyldimethylsilyl triflate (132 µl, 0.60 mmol) was added slowly and the solution stirred at this temperature for 1 hour. EtOAc (10 ml) and water (10 ml) were added and the reaction allowed to warm to room temperature where the organic liquors were washed with 0.3M $KHSO_4$ (10 ml), water (10 ml) and brine (10 ml). Concentration of the liquors under reduced pressure gave the *TBS ether* as an oil, which was used in the next step without purification.

A stirred solution of the TBS ether in acetone (3 ml) was treated with 2,2-dimethoxypropane (1 ml) and boron trifluoride etherate (10 µl) for 2 hours at room

temperature. The solvent was removed *in vacuo*, the residue taken up in DCM (5 ml) and washed with sat. aq. $NaHCO_3$ (5 ml), brine (5 ml), and dried over anhydrous Na_2SO_4. Concentration *in* vacuo followed by column chromatography eluting with petrol-EtOAc (20:1) gave *the acetal* **89** as an oil (150 mg, 62%). R_F (petrol-EtOAc 8:1) 0.67; $[\alpha]_D^{21}$ -2.39 (c 0.96 $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 1698 (C=O), 1385 (CMe_2), 1253 ($SiMe_2$), 1084 (Si-O), 836 ($SiMe_2$); δ_H (250 MHz, $CDCl_3$) 0.44 (6H, s, Si*Me*$_2$), 0.86 (9H, s, SiC*Me*$_3$), 1.22 (3H, s, *Me*-acetal), 1.29 (3H, d, *J* 6.0, CH*Me*), 1.38 (3H, s, *Me*-acetal), 1.44 (9H, s, OC*Me*$_3$), 1.45, 1.46 (6H, 2xs, *Me*-oxazolidine) and 3.65-4.06, (6H, m, 4xC*H* and C*H*$_2$OTBS); δ_C (62.9 MHz, $CDCl_3$) -5.6 (CH_3, Si*Me*$_2$), 18.2 (C, SiCMe$_3$), 20.0 (brCH$_3$, CH*Me*), 25.7 (CH_3, SiC*Me*$_3$), 26.6, 27.1 (brCH$_3$, 2x*Me*-acetal and 2x*Me*-oxazolidine), 28.3 (CH_3, OC*Me*$_3$), 53.8 (CH, *C*HMe), 63.7 (CH_2, *C*H$_2$OTBS), 76.5, 77.5 (2xCH, *CHC*HCH$_2$), 79.5 (C, OCMe$_3$), 80.8 (CH, *C*HCHMe), 94.8 (C, *C*-oxazolidine), 109.36 (C, *C*-acetal) and 151.8 (C, *C*=O); *m/z* (F.A.B.) 460 [$(MH)^+$, 6.6%], 444 (14), 344 (31), 57 (53); [Found; $(MH)^+$, 459.30331. $C_{23}H_{46}NO_6Si$ requires MH, 459.30162].

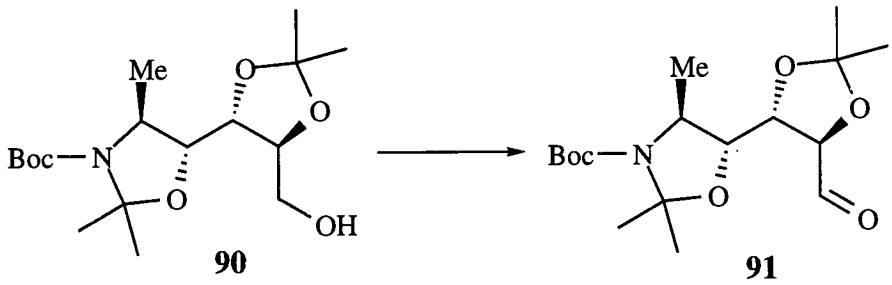
*5.2.25 (4S, 5R)-N-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1S, 2S)-3-hydro xy-1-2-*iso*propylidenepropan-1-yl]oxazolidine* ***90***



A stirred solution of the TBS ether **89** (150 mg, 0.33 mol) in THF (4 ml) was treated with TBAF (1M solution in THF, 0.51 ml, 0.51 mmol) for 1 hour at room temperature. The solvent was removed *in vacuo*, the residue taken up in ether (5 ml) and washed with water (5 ml), dilute HCl (5 ml), brine (5 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and column chromatography of the residue eluting with petrol-ether (1:1) gave the *primary alcohol* **90** as an oil (90 mg, 80%). R_F (petrol-EtOAc 5:1) 0.65; $[\alpha]_D^{23}$ -6.12 (c 0.57 in $CHCl_3$); υ_{max}/cm^{-1} (film, NaCl) 3462br (OH), 1694 (C=O), 1391 (CMe_2), 1080 (C-O); δ_H (200 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.0, CH*Me*), 1.40 (6H, br.s, 2x*Me*-acetal), 1.45 (12H, br.s, OC*Me*$_3$ and *Me*-oxazolidine), 1.56 (3H, s, *Me*-oxazolidine) and

3.59-4.14 (6H, m, 4xC*H* and CH_2OH); δ_C (50.1 MHz, $CDCl_3$) 18.2 (CH_3, CH*Me*), 25.3-25.7 (4xCH_3, 2x*Me*-acetal and 2x*Me*-oxazolidine) 27.0 (CH_3, OC*Me*$_3$), 52.7 (CH, *C*HMe), 60.8 (CH_2, *C*H_2OH), 75.0, 75.7 (2xCH, *CHC*HCH$_2$), 78.5 (C, O*C*Me$_3$), 78.8 (CH, *C*HCHMe), 93.4 (C, *C*-oxazolidine), 108.3 (C, *C*-acetal) and 150.7 (C, *C*=O); *m/z* (F.A.B.) 346 [(MH)$^+$, 19.6%], 330 (26), 57 (61); [Found; (MH)$^+$, 346.22249. $C_{17}H_{32}NO_6$ requires MH, 346.22296].

*5.2.26 (4S, 5R)-*N*-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1S, 2R)-1-*2*-iso propylidene-3-oxo-propan-1-yl]oxazolidine **91***

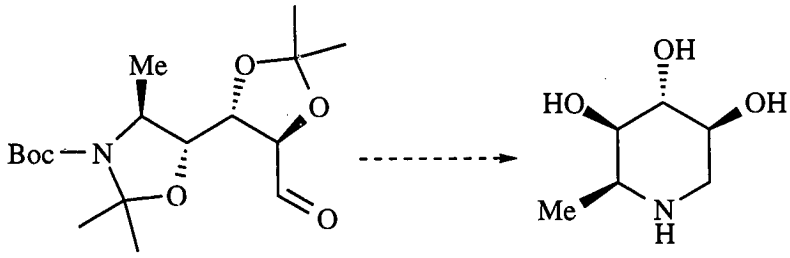


90 **91**

A solution of NaBr (4 mg, 0.04 mmol) and BTAC (3 mg, 0.02 mmol) in sat. aq. $NaHCO_3$ (0.87 ml) was added to a vigorously stirred solution of the alcohol **90** (90 mg, 0.26 mmol) and TEMPO (2 mg, 0.01 mmol) in DCM (1.5 ml) at 0°C. A solution of sodium hypochlorite (1.12M, 0.30 mmol) in sat. aq $NaHCO_3$ (0.52 ml) and brine (1.04 ml) were added dropwise over 45 minutes and stirring was continued for a further 45 minutes at 0°C and then at room temperature for 15 minutes. The layers were separated, the aqueous layer extracted with DCM (2 x 3 ml) and the combined organic fractions washed with sat. aq. $NaHCO_3$ (5 ml), brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude *aldehyde* **91** (74 mg, 83%). υ_{max}/cm^{-1} (film, NaCl) 1736 (C=O aldehyde), 1693 (C=O urethane), 1392 (CMe_2), 1097 (C-O); δ_H (200 MHz, $CDCl_3$) 1.19 (3H, s, *Me*-acetal), 1.28 (3H, d, *J* 6.0, CH*Me*), 1.35 (3H, s, *Me*-acetal), 1.41-1.43 (12H, br.s, O*C*Me$_3$ and *Me*-oxazolidine), 1.53 (3H, s, *Me*-oxazolidine), 3.75-3.80 (2H, br.m, C*HCH*Me), 4.13 (1H, dd, *J* 7.0, 3.5, C*H*CHCHO), 4.28 (1H, dd, *J* 7.0, 1.5, C*H*CHO) and 9.74 (1H, d, *J* 1.5, C*H*O); δ_C (50.1 MHz, $CDCl_3$) 18.1 (CH_3, CH*Me*), 24.8-25.5 (brCH_3, 2x*Me*-acetal and 2x*Me*-oxazolidine), 27.0 (CH_3, OC*Me*$_3$), 52.6 (CH, *C*HMe), 77.5 (C, O*C*Me$_3$), 78.6, 78.8 (3xCH, *CHCHCHCHO*), 93.9 (C, *C*-oxazolidine), 110.5 (C, *C*-acetal), 150.6 (C, *C*=O urethane) and 199.8 (C, *C*=O aldehyde); *m/z* (F.A.B.)

344 [$(MH)^+$, 10.6%], 244 (82), 57 (63); [Found: $(MH)^+$, 344.20665. $C_{17}H_{30}NO_6$ requires MH, 344.20731].

5.2.27 Attempted ring closure of (4S, 5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[(1S, 2R)-1-2-isopropylidene-3-oxo-propan-1-yl]oxazolidine ***91*** via *the bisulfite adduct* ***92***

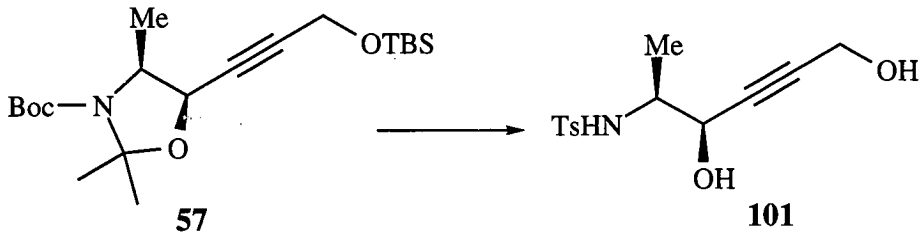


91 **93**

A cold (0°C) suspension of the aldehyde **91** (70 mg, 0.2 0mmol) in water (2 ml) was saturated with SO_2, then allowed to stir at 40°C for 2 days before cooling to 0°C. Methanol (1.5 ml) was added and the mixture re-saturated with SO_2 and allowed to stand for 12 hours at 0 °C, no precipitate resulted hence the solvent was removed *in vacuo*. The residue was dissolved in water (2 ml) and treated with $Ba(OH)_2.8H_2O$ (62 mg, 0.19 mmol) for 4 hours. The precipitate was filtered, dissolved in water (3 ml) and stirred under an atmosphere of hydrogen in the presence of palladium (5% on C, 5 mg) for 24 hours. Removal of the catalyst by filtration through a plug of Celite and concentration of the filtrate under reduced pressure gave an oily residue which was complex by ^1H nmr spectroscopy and did not illustrate the presence of a cyclised ring.

5.3 EXPERIMENTAL FOR CHAPTER 4. THE SYNTHESIS OF 1,1-*BIS*-HYDROXYMETHYL-1,5-DIDEOXY-1,5-IMINO-L-FUCITOL

5.3.1 (2S, 3R)-N-(4-toluenesulfonyl)-2-amino-3,6-dihydroxy-hex-4-yne ***101***



57 **101**

Method 1.

The oxazolidine **57** (52 mg, 0.14 mmol) was dissolved in EtOAc (1 ml), 3M HCl (1ml) added and the reaction stirred for 24 hours. Concentration under reduced pressure gave an oily residue which was then suspended in DCM (1 ml) and cooled to 0°C. Triethylamine (59 µl, 0.42 mmol) was added, followed by slow addition of tosyl chloride (30 mg, 0.15 mmol) and the solution warmed to room temperature and stirred for 26 hours. EtOAc (5 ml) and water (5 ml) were added, the layers separated and the organic liquors washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography eluting with EtOAc-petrol (2:1) to give the *N-Tosyl amide* **101** (22 mg, 56%) as a solid.

Method 2.

The oxazolidine **57** (56 mg, 0.15 mmol) was treated with trifluoroacetic acid (99%, 0.5 ml) at 0°C with stirring for 1 hour at room temperature. Concentration under reduced pressure gave an oily residue, which was suspended in DCM (1 ml) and cooled to 0°C. Triethylamine (70 µl, 0.67 mmol) was added followed by tosyl chloride (32 mg, 0.17 mmol) and the mixture stirred for 26 hours at room temperature. The solvent was removed *in vacuo* and the residue subjected to column chromatography eluting with EtOAc-petrol (2:1) to give the *N-Tosyl amide* **101** as a white solid (18 mg, 44%).

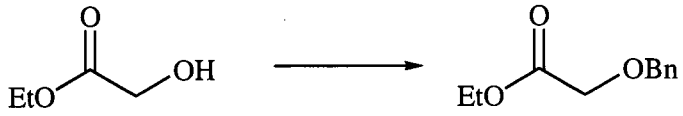
Method 3.

Trifluoroacetic acid (99%, 0.5 ml) was added to the oxazolidine **57** (23 mg, 0.06 mmol) and the mixture stirred for 30 minutes at room temperature. Water (1 ml) was added, and the mixture was concentrated under reduced pressure and the residue dissolved in DCM (0.5 ml) and 1,4-dioxane (5 ml). Triethylamine (18 µl, 0.13 mmol)

was added to the stirred solution at 0°C followed by tosyl chloride (13 mg, 0.07 mmol) and stirring was continued at room temperature for 26 hours. EtOAc (5 ml) and water (5 ml) were added and the organic liquors were separated and washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with EtOAc-petrol (2:1) gave the *N-Tosyl amide* **101** as a white solid (8 mg, 51%).

R_F 0.25; υ_{max}/cm^{-1} (film, IR card) 3273br (OH), 1325, 1159 (SO_2-N), 1091 (C-O); δ_H (250 MHz, DMSO) 0.89 (3H, d, *J* 6.5, CH*Me*), 2.34 (3H, s, *Me*-aryl), 3.21 (1H, m, C*H*Me), 4.01 (2H, dd, *J* 6.0, 2.0, C*H*$_2$OH), 4.17 (1H, m, C*H*OH), 5.13 (1H, t, *J* 6.0, CH$_2$O*H*), 5.54 (1H, d, *J* 6.0, CHO*H*), 7.38 (2H, d, *J* 8.5, C*H*-aryl), 7.60 (1H, d, *J* 8.0, N*H*) and 7.70 (2H, d, *J* 8.5, C*H*-aryl); δ_C (62.9 MHz, DMSO) 14.8 (CH_3, CH*Me*), 21.1 (CH_3, *Me*-aryl), 49.1 (CH_2, *C*H$_2$OH), 54.1 (CH, *C*HMe), 83.9, 84.7 (2xC, *C*-acetylene), 126.6, 129.6 (CH, *aryl*), 138.9 and 142.6 (2xC, *aryl*); *m/z* (F.A.B.) 284 [(MH)$^+$, 100%], 268 (39), 198 (61); [Found: (MH)$^+$, 284.09537. $C_{13}H_{18}NO_4S$ requires MH, 283.09566].

*5.3.2 Benzyloxy-acetic acid ethyl ester **109***



108 **109**

To a solution of ethyl glycolate **108** (12.5 ml, 0.13 mol) in ether (220 ml) was added silver (I) oxide (33.60 g, 0.15 mol) and benzyl bromide (17.8 ml, 0.15 mol) and the resulting black suspension brought to reflux for 24 hours. The solid was removed by filtration through a pad of Celite, washed with ether (2 x 40 ml) and the combined filtrates concentrated *in vacuo*. The crude product was subjected to column chromatography eluting with petrol-ethyl acetate (5:1) to yield the *benzyl ether* **109** as an oil (20.71 g, 82%). R_F 0.38; υ_{max}/cm^{-1} (film, NaCl) 1750 (C=O), 1201, 1128 (C-O); δ_H (250 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0, *Me*CH$_2$), 4.08 (2H, s, C*H*$_2$OBn), 4.22 (2H, q, *J* 7.0, C*H*$_2$Me), 4.62 (2H, s, C*H*$_2$Ph) and 7.25-7.38 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 14.0 (CH_3, CH$_2$*Me*), 60.7 (CH_2, *C*H$_2$Me), 67.0 (CH_2, *C*H$_2$OBn), 73.2 (CH_2, *C*H$_2$Ph), 127.9, 128.3 (CH, *Ph*), 136.9 (C, *Ph*) and 170.2 (C, *C*=O); *m/z* (F.A.B.) 195 [(MH)$^+$, 100%], 181 (89), 149 (3), 77 (18); [Found: (MH)$^+$, 195.10212. $C_{11}H_{15}O_3$ requires MH, 195.10221).

5.3.3 Benzyloxyacetaldehyde 110

109 **110**

A cooled (-78°C) stirred solution of the ester **109** (14.60 g, 0.08 mol) in DCM (150 ml) under a nitrogen atmosphere was treated with di-*iso*butylaluminium hydride (1M solution in toluene, 75 ml, 0.08 mol) by slow addition and stirring was continued at this temperature for 2 hours. After addition of sat. aq. NH_4Cl (50 ml) and 1M HCl (50 ml) the resulting suspension was warmed to room temperature and the organic phase separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde. Column chromatography of the residue eluting with petrol-ethyl acetate (4:1) gave the *aldehyde*[122] **110** (6.38 g, 60%). R_F (hexane-EtOAc 2:1) 0.35; υ_{max}/cm^{-1} (film, NaCl) 1736 (C=O), 1116 (C-O); δ_H (200 MHz, $CDCl_3$) 4.09 (2H, d, *J* 0.5Hz, CH_2CHO), 4.62 (2H, s, CH_2Ph), 7.25-7.41 (5H, m, *Ph*) and 9.70 (1H, t, *J* 0.5, CH_2CHO); δ_C (50.1 MHz, $CDCl_3$) 73.4 (CH_2, CH_2Ph), 75.1 (CH_2, CH_2OBn), 127.6, 127.8, 128.0, 128.2, 128.4 (CH, *Ph*), 136.7 (C, *Ph*) and 200.2 (C, *C*=O); *m/z* (F.A.B.) 151 [$(MH)^+$, 1.2%], 149 (5), 107 (4), 91 (100); [Found: $(MH)^+$, 151.07570. $C_9H_{11}O_2$ requires MH, 151.07590].

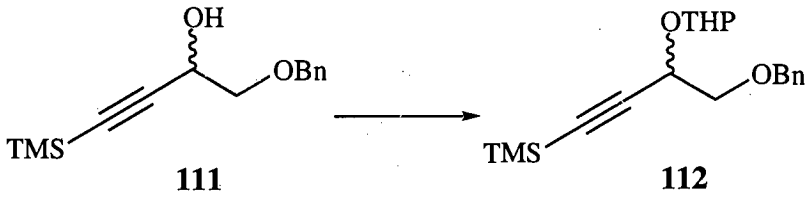
5.3.4 (3RS)-4-benzyloxy-3-hydroxy-1-trimethylsilylbut-1-yne 111

110 **111**

A solution of *bis*-trimethylsilylacetylene (8.04 g, 0.05 mol) in THF (100 ml) was cooled to -30°C under nitrogen and methyl lithium (1.5M solution in ether as a complex with LiBr, 32 ml, 0.05 mol) was added rapidly. The solution was stirred at room temperature for 1 hour then cooled to 0°C whereupon a solution of the aldehyde **110** (3.93 g, 0.03 mol) in THF (20 ml) was added dropwise over 15 minutes. Stirring was continued at room temperature for a further 2 hours then the reaction was quenched by addition of the reaction mixture to ice cold sat. aq. NH_4Cl (50 ml). After separation of the two phases the aqueous layer was extracted with ether (2 x 40 ml)

and the combined organic extracts washed with sat. aq. $NaHCO_3$ (40 ml), brine (40 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with petrol-ethyl acetate (6:1) gave *racemic TMS propargyl alcohol*[105] **111** (4.74 g, 75%). R_F (hexane-EtOAc 5:1) 0.29; υ_{max}/cm^{-1} (film, NaCl) 3419br (OH), 2171 (acetylene), 1093 (C-O), 843 ($SiMe_3$); δ_H (250 MHz, $CDCl_3$) 0.17 (9H, s, Si*Me*$_3$), 2.55 (1H, br.s, O*H*), 3.55 (1H, dd, *J* 10.0, 7.5, C*H*$_2$OBn), 3.64 (1H, dd, *J* 10.0, 3.5, C*H*$_2$OBn), 4.56 (1H, dd, *J* 7.5, 3.5, C*H*CH$_2$OBn) 4.60 (2H, s, C*H*$_2$Ph) and 7.28-7.39 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) -0.4 (CH_3, Si*Me*$_3$), 62.0 (CH, *C*HOH), 73.2 (CH_2, *C*H$_2$Ph), 76.4 (CH_2, *C*H$_2$OBn), 90.4, 102.9 (2xC, *C*-acetylene), 127.6, 127.7, 127.7 (CH, *Ph*), and 137.5 (C, *Ph*); *m/z* (F.A.B.) 249 [$(MH)^+$, 1.3%], 247 (2), 91 (93), 73 (100); [Found: $(MH)^+$, 249.13056. $C_{14}H_{21}O_2Si$ requires MH, 249.13108].

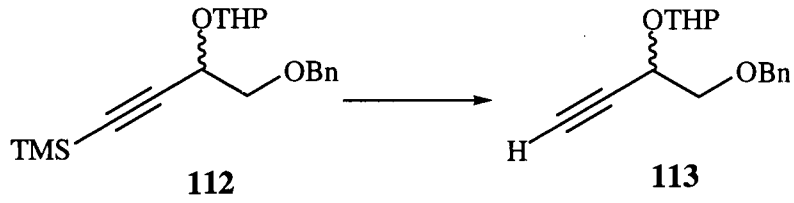
*5.3.5 (3*RS*)-4-benzyloxy-3-tetrahydropyran-2-yloxy-1-trimethylsilylbut-1-yne* ***112***



A stirred solution of the racemic propargyl alcohol **111** (240 mg, 0.99 mmol) in DCM (3 ml) was treated with 3,4-dihydro-2*H*-pyran (117 µl, 1.29 mmol) and *para*-toluenesulfonic acid (9 mg, 5 mol%) and stirring continued for 1 hour. The mixture was diluted with ether (5 ml) and partitioned between a mix of brine (3 ml), sat. aq. $NaHCO_3$ (3 ml) and water (6 ml). The organic extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was subjected to column chromatography eluting with petrol-ether (12:1) to give the *THP-ether* **112** as an oil (276 mg, 84%). R_F (petrol-ether 9:1) 0.37-0.47; υ_{max}/cm^{-1} (film, IR card) 2171 (acetylene), 2148 ($SiMe_3$), 1118, 1075 (C-O), 839 ($SiMe_3$); δ_H (250 MHz, $CDCl_3$) 0.18 (9H, s, Si*Me*$_3$), 1.48-1.90 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$), 3.47-4.03 (4H, m, C*H*$_2$OBn, and CH$_2$C*H*$_2$O), 4.53-4.63 (1H, m, C*H*OTHP), 4.66 (2H, s, C*H*$_2$Ph), 4.68-5.04 (1H, m, O-C*H*-O) and 7.23-7.40 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) -0.3 (CH_3, Si*Me*$_3$), 18.6, 25.3, 30.2 (3xCH$_2$, *C*H$_2$*C*H$_2$*C*H$_2$), 61.7 (CH_2, CH$_2$*C*H$_2$O), 64.8, 67.1 (CH, *C*HOTHP diastereomers), 72.1, 73.1 (2xCH$_2$, *C*H$_2$Ph and *C*H$_2$OBn), 91.1 (C, *C*-acetylene), 94.9, 98.5 (CH, O-*C*H-O diastereomers), 101.7 (C, *C*-acetylene), 127.3, 127.4, 128.2 (CH, *Ph*) and 138.1 (C, *Ph*); *m/z* (F.A.B.) 333 [$(MH)^+$, 6.3%],

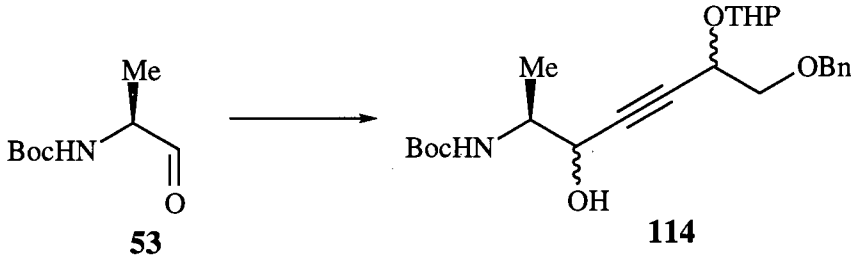
247 (1), 231 (5), 85 (100), 73 (19); [Found: $(MH)^+$, 333.18944. $C_{19}H_{29}O_3Si$ requires MH, 333.18860].

5.3.6 (2RS)-1-benzyloxy-2-tetrahydropyran-2-yloxybut-3-yne ***113***



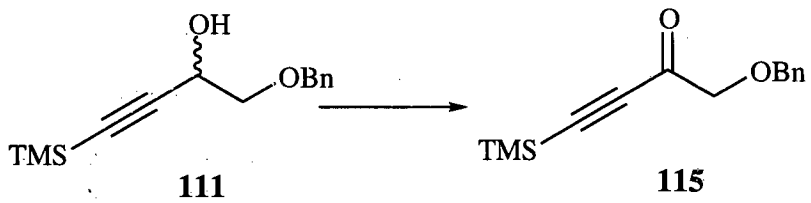
A stirred solution of the TMS-acetylene **112** (276 mg, 0.83 mmol) in methanol (8 ml) was treated with potassium carbonate (172 mg, 1.25 mmol) and the mixture stirred at room temperature for 2 hours. Ether (5 ml) and water (5 ml) were added and the aqueous layer extracted with ether (2 x 5 ml), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with petrol-EtOAc (5:1) gave the *terminal acetylene* **113** (196 mg, 90%). R_F (hexane-EtOAc 5:1) 0.56; υ_{max}/cm^{-1} (film, NaCl) 3287 (CH acetylene), 2114 (acetylene), 1123, 1075 (C-O); δ_H (250 MHz, $CDCl_3$) 1.52-1.84 (6H, m, $CH_2CH_2CH_2$), 2.41 (1H, d, *J* 2.0, *CH*-acetylene), 3.49-3.90 (4H, m, CH_2OBn and CH_2CH_2O), 4.55-4.88 (3H, m, CH_2Ph and *CH*OTHP), 5.00-5.03 (1H, t, *J* 3.0, O-*CH*-O) and 7.25-7.39 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 18.8, 25.2, 30.2 ($3xCH_2$, $CH_2CH_2CH_2$), 61.7 (CH_2, CH_2CH_2O), 64.2, 66.3 (CH, O-*C*H-OTHP), 71.9, 72.9 (CH_2, CH_2Ph and CH_2OBn), 74.1 (CH, *C*H-acetylene), 80.2 (C, *C*-acetylene), 95.2, 98.8 (CH, O-C*H*-O diastereomers), 127.4, 128.2 (CH, *Ph*) and 138.0 (C, *Ph*); *m/z* (F.A.B.) 261 [$(MH)^+$, 11.5%], 85 (100); [Found: $(MH)^+$, 261.14803. $C_{16}H_{21}O_3$ requires MH, 261.14907].

5.3.7 (2S, 3RS, 6RS)-N-(tert-butoxycarbonyl)-2-amino-3-hydroxy-6-tetrahydropyran-2-yloxy-7-benzyloxyhept-4-yne ***114***



To a cooled (-100°C) stirred solution of the terminal acetylene **113** (196 mg, 0.75 mmol) in THF (8 ml) and ether (2 ml) was added *n*-butyllithium (1.44M in hexanes, 0.52 ml, 0.75 mmol) dropwise and stirring continued for 5 minutes. A solution of *N*-Boc-L-alaninal **53** (63 mg, 0.36 mmol) in THF (2 ml) was added slowly and after a further 5 minutes the reaction was quenched by addition of sat. aq. NH_4Cl (5 ml) and the resulting suspension warmed to room temperature. The aqueous layer was extracted with ether (2 x 5 ml) and the combined organic phases dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with petrol-EtOAc (2:1) yielded the unreacted terminal acetylene **113** (137 mg) and the *β-amino alcohol* **114** (89 mg, 56%). R_F (hexane-EtOAc 2:1) 0.30; υ_{max}/cm^{-1} (film, IR card) 3384br (OH), 1691 (C=O), 1364 (CMe_3), 1166, 1114, 1022 (C-O); δ_H (250 MHz, $CDCl_3$) 1.13-1.23 (3H, m, CH*Me*), 1.41 (9H, s, OC*Me*$_3$), 1.46-1.79 (6H, m, $CH_2CH_2CH_2$), 3.46-3.87 (6H, m, CH_2OBn, CH_2CH_2O, CHMe and O*H*), 4.34-4.97 (6H, m, CH_2Ph, O-C*H*-O, C*H*OTHP, N*H*, C*H*OH) and 7.28-7.35 (5H, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 15.9 (CH_3, CH*Me*), 18.7, 25.2, 30.1 (3xCH_2, $CH_2CH_2CH_2$), 28.2 (CH_3, OC*Me*$_3$), 50.5 (CH, *C*HMe), 61.6 (CH_2, CH_2CH_2O), 64.4, 65.5 (CH, *C*HOH diastereomers), 71.9, 73.2 (2xCH_2, CH_2Ph and CH_2OBn), 79.5, 82.1, 84.6 (3xC, 2x*C*-acetylene and O*C*Me$_3$), 95.1, 98.9 (2xCH, *C*HOTHP and O-*C*H-O), 127.5, 128.2 (CH, *Ph*), 137.8 (C, *Ph*) and 155.7 (C, *C*=O); *m/z* (F.A.B.) 434 [$(MH)^+$, 3.1%], 85 (20), 57 (13); [Found: $(MH)^+$, 434.25401. $C_{24}H_{36}NO_6$ requires MH, 434.25426].

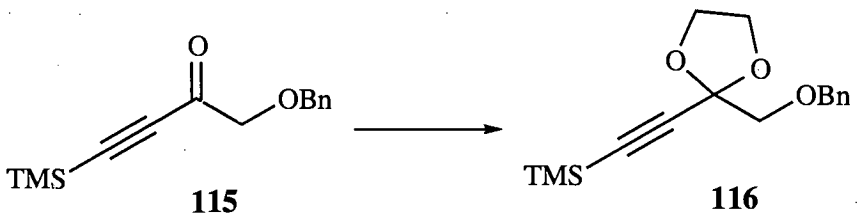
5.3.8 4-benzyloxy-1-trimethylsilyl-3-oxobut-1-yne ***115***



A solution of NaBr (240 mg, 2.41 mmol, 10 mol%) and BTAC (220 mg, 1.20 mmol, 5 mol%) in sat. aq. $NaHCO_3$ (40 ml) was added to a vigorously stirred solution of the propargyl alcohol **111** (5.87 g, 21.12 mmol) and TEMPO (39 mg, 0.26 mmol, 1 mol%) in DCM (60 ml). The bi-phasic mixture was cooled to 0°C and a solution of sodium hypochlorite (0.86M, 36 ml, 30% excess), sat. aq. $NaHCO_3$ (24 ml) and brine (48 ml) were added dropwise over 1 hour. Stirring was continued for a further 1 hour at 0°C and then at room temperature for a further 2 hours. The phases were separated,

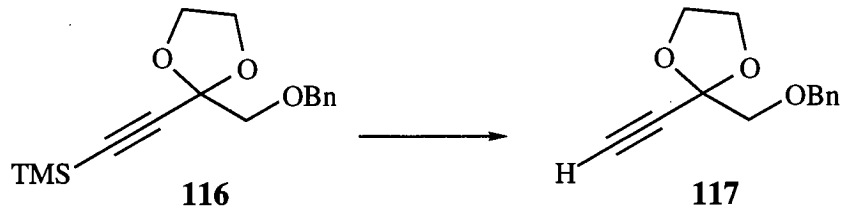
the aqueous layer extracted with DCM (2 x 30 ml) and the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 ml), brine (50 ml), dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to yield the crude *α,β-acetylenic ketone* **115** (5.74 g, 97%). υ_{max}/cm^{-1} (film, NaCl) 2150 (acetylene), 1678 (C=O), 1251 ($SiMe_3$), 1080 (C-O), 846 ($SiMe_3$); δ_H (250 MHz, $CDCl_3$) 0.24 (9H, s, Si*Me*$_3$), 4.22 (2H, s, C*H*$_2$OBn), 4.63 (2H, s, C*H*$_2$Ph) and 7.27-7.37 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) -1.1 (CH_3, Si*Me*$_3$), 73.2 (CH_2, *C*H$_2$Ph), 77.5 (CH_2, *C*H$_2$OBn), 99.6, 101.1 (2xC, *C*-acetylene), 127.7, 127.8, 128.3 (CH, *Ph*), 136.9 (C, *Ph*) and 184.5 (C, *C*=O); *m/z* (E.I.) 246 (M^+, 6.3%), 172 (15), 139 (78), 73 (100); (Found: M^+, 246.10761. $C_{14}H_{18}O_2Si$ requires M, 246.10728).

5.3.9 4-benzyloxy-3,3-ethylenedioxy-1-trimethylsilylbut-1-yne ***116***



Ethylene glycol (70 ml) and trimethylsilyl chloride (7.3 ml) were added to a stirred solution of the α,β-acetylenic ketone **115** (3.55 g, 14.41 mmol) in DCM (35 ml) under a nitrogen atmosphere. The solution was stirred at room temperature for 48 hours whereafter the reaction was quenched by addition of sat. aq. $NaHCO_3$ (30 ml). The phases were separated and the organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue subjected to column chromatography eluting with petrol-ether (10:1) to yield the *1,3-dioxolane* **116** (3.69 g, 88%). R_F (hexane-ether 5:1) 0.28; (Found: C, 68.81, H, 8.66; $C_{16}H_{22}O_3Si$ requires C, 68.68; H 8.49%); υ_{max}/cm^{-1} (film, NaCl) 1251 ($SiMe_3$), 1103 (C-O), 843 ($SiMe_3$); δ_H (250 MHz, $CDCl_3$) 0.18 (9H, s, Si*Me*$_3$), 3.70 (2H, s, C*H*$_2$OBn), 3.99-4.14 (4H, m, C*H*$_2$C*H*$_2$), 4.70 (2H, s, C*H*$_2$Ph) and 7.26-7.39 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) -0.5 (CH_3, Si*Me*$_3$), 65.1 (CH_2, *C*H$_2$CH$_2$), 72.8 (CH_2, *C*H$_2$OBn) 73.6 (CH_2, *C*H$_2$Ph), 89.8 (C, *C*-ketal), 100.9, 101.6 (2xC, *C*-acetylene), 127.4, 127.4, 128.1 (CH, *Ph*) and 137.9 (C, *Ph*); *m/z* (F.A.B.) 291 [$(MH)^+$, 15.5%), 290 (8), 213 (20), 169 (100), 97 (74), 91 (12); [Found: $(MH)^+$, 291.14215. $C_{16}H_{23}O_3Si$ requires MH, 291.14165].

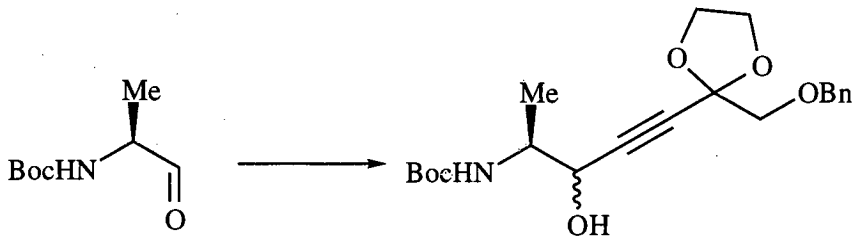
5.3.10 1-benzyloxy-2,2-ethylenedioxybut-3-yne ***117***



116 **117**

Potassium carbonate (2.61 g, 18.9 mmol) was added to a stirred solution of TMS-acetylene **116** (3.65 g, 12.5 mmol) in methanol (100 ml) and stirring continued for 2 hours at room temperature. Ether (50 ml) and water (30 ml) were added and the aqueous layer was separated and extracted with ether (2 x 20 ml). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-EtOAc (5:1) gave the *terminal acetylene* **117** (2.56 g, 93%). R_F (petrol-EtOAc 6:1) 0.31; υ_{max}/cm^{-1} (film, NaCl) 3276 (acetylene CH), 2110 (acetylene), 1104 (C-O); δ_H (250 MHz, $CDCl_3$) 2.56 (1H, s, C*H*-acetylene), 3.70 (2H, s, CH_2OBn), 4.01-4.14 (4H, m, CH_2CH_2), 4.70 (2H, s, CH_2Ph) and 7.27-7.37 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 65.0 (CH_2, CH_2CH_2), 72.7 (CH_2, CH_2OBn), 72.9 (CH, *C*H-acetylene), 73.7 (CH_2, CH_2Ph), 78.0 (C, *C*-ketal), 101.5 (C, *C*-acetylene), 127.4, 127.5, 128.2 (CH, *Ph*) and 137.7 (C, *Ph*); *m/z* (F.A.B.) 219 [$(MH)^+$, 52.7%], 193 (33), 97 (97), 91 (68); [Found: $(MH)^+$, 219.10268. $C_{13}H_{15}O_3$ requires MH, 219.10212].

5.3.11 (2S, 3SR)-N-(tert-butoxycarbonyl)-2-amino-7-benzyloxy-6,6-ethylenedioxy-3-hydroxyhept-4-yne ***118a/b***



53 **118a/b**

Method 1, Use of the lithium acetylide in THF:-

To a stirred solution of acetylene **117** (283 mg, 1.30 mmol) in THF (5 ml) at -78°C was added slowly *n*-butyllithium (1.34M in hexanes, 1.0 ml, 1.34 mmol) under a nitrogen atmosphere and stirring continued at that temperature for 1 hour. A solution of

N-Boc-L-alaninal **53** (100 mg, 0.58 mmol) in THF (2 ml) was then added dropwise and after 1 hour the reaction was quenched by addition to ice cold 1M NaH_2PO_4 (10 ml) with swirling. The mixture was extracted with ether (3 x 5 ml), and the combined organic phases washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give an oil. Column chromatography of the residue eluting with hexane-EtOAc (6:1) gave the recovered acetylene **117** (193 mg) and the *β-amino alcohols* **118a/b** (133 mg, 55%).

Method 2. Use of the lithium acetylide in ether:-

To a stirred solution of acetylene **117** (282 mg, 1.30 mmol) in ether (5 ml) under a nitrogen atmosphere at -78°C was added slowly *n*-butyllithium (1.48M in hexanes, 0.9 ml, 1.33 mmol) and the resultant suspension stirred for 1 hour at this temperature. A solution of *N*-Boc-L-alaninal **53** (100 mg, 0.58 mmol) in ether (2 ml) was added dropwise and the mixture stirred at -78°C for 4 hours before pouring into ice cold 1M NaH_2PO_4 (20 ml) and extracting with ether (2 x 5 ml). The organic liquors were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with hexane-EtOAc (6:1) gave the recovered acetylene **117** (197 mg) and the *β-amino alcohols* **118a/b** (104 mg, 44%).

Method 3. Use of the Grignard acetylide formed via *transmetallation:-*

A cold (-78°C) and stirred solution of the acetylene **117** (290 mg, 1.33 mmol) in THF (5 ml) under a nitrogen atmosphere was treated with *n*-butyllithium (1.34M in hexanes, 1.0 ml, 1.34 mmol) and stirring was continued for 1 hour. A slurry of magnesium bromide (275 mg, 1.49 mmol) in THF (2 ml) was added *via* canula and after 20 minutes was followed by addition of *N*-Boc-L-alaninal **53** (103 mg, 0.59 mmol) in THF (2 ml). The mixture was stirred for 1 hour at -78°C and then quenched by addition of sat. aq. NH_4Cl (5 ml), extracted with ether (2 x 5 ml) and the combined organic extracts dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue (hexane-EtOAc 6:1) gave the recovered acetylene **117** (180 mg) and the *β-amino alcohols* **118a/b** (131 mg, 56%).

Method 4. Use of the Grignard acetylide at room temperature:-

Ethylmagnesium bromide (1M in THF, 1.30 ml, 1.30 mmol) was added dropwise to a stirred solution of the acetylene **117** (290 mg, 1.33 mmol) in THF (3 ml) at 0°C under a nitrogen atmosphere. After stirring at room temperature for 1 hour, a solution of *N*-Boc-L-alaninal **53** (105 mg, 0.60 mmol) in THF (2 ml) was added dropwise and the

reaction mixture stirred for 1 hour. The reaction was quenched by dropwise addition of sat. aq. NH_4Cl (5 ml), extracted with ether (2 x 5 ml), and the combined organic extracts dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography eluting with hexane-EtOAc (6:1) gave recovered acetylene **117** (187 mg) and the *β-amino alcohols* **118a/b** (162 mg, 69%).

Method 5. Use of the Grignard acetylide at low temperature:-

A stirred solution of the acetylene **117** (285 mg, 1.31 mmol) in THF (5 ml) was cooled to 0°C and ethylmagnesium bromide (1M in THF, 1.3 ml, 1.30 mmol) added dropwise and the resulting solution stirred at room temperature for 1 hour then cooled to -78°C. A solution of *N*-Boc-L-alaninal **53** (102 mg, 0.59 mmol) in THF (2 ml) was added dropwise, stirring continued for 1 hour whereafter the reaction was quenched with sat. aq. NH_4Cl (5 ml). Extraction of the aqueous layer with ether (2 x 5 ml) followed by drying of the organic extracts with anhydrous Na_2SO_4 and removal of the solvent under reduced pressure gave an oily residue which was subjected to column chromatography yielding recovered acetylene **117** (207 mg) and the *β-amino alcohols* **118a/b** (133 mg, 59%).

Method 6. Use of the Grignard acetylide at room temperature-different addition:-

A stirred solution of acetylene **117** (292 mg, 1.34 mmol) in THF (3 ml) was cooled to 0°C and ethylmagnesium bromide (1M in THF, 1.35 ml, 1.35 mmol) added dropwise and stirring continued at room temperature for 1 hour. The resulting solution was added to a cold (-78°C) solution of *N*-Boc-L-alaninal **53** (101 mg, 0.58 mmol) in THF (5 ml) and stirred for 1 hour at this temperature and for a further 30 minutes at room temperature. The reaction was quenched with sat. aq. NH_4Cl (10 ml), extracted with ether (2 x 5 ml) and washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue yielded recovered acetylene **117** (166 mg) and the *β-amino alcohols* **118a/b** (175 mg, 77%).

Method 7. Use of the copper acetylide:-

Ethyl magnesium bromide (1M in THF, 1.30 ml, 1.30 mmol) was added dropwise to a solution of acetylene **117** (282 mg, 1.29 mmol) in THF (3ml) at 0°C under a nitrogen atmosphere. After stirring for 1 hour at room temperature the solution was transferred *via* canula to a cooled (-78°C) solution of copper iodide (370 mg, 1.94 mmol) and dimethyl sulfide (1 ml) in THF (5 ml). Stirring was continued at -30°C for 30 minutes then cooled to -78°C whereupon a solution of *N*-Boc-L-alaninal **53** (102

mg, 0.59 mmol) in THF (2 ml) was added dropwise. The resulting suspension was stirred at room temperature for 3 hours, quenched by addition of sat. aq. NH_4Cl (5 ml) and extracted with ether (2 x 5 ml). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue (hexane-EtOAc 6:1) gave the recovered acetylene **117** (204 mg) and the *β-amino alcohols* **118a/b** (100 mg, 44%).

Method 8. Use of the zinc acetylide:-

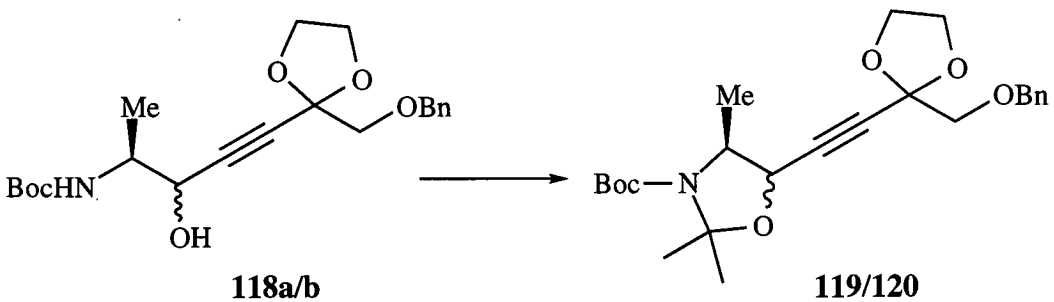
A cold (-78°C) and stirred solution of the acetylene **117** (283 mg, 1.30 mmol) in THF (5 ml) under a nitrogen atmosphere was treated with *n*-butyllithium (1.38M in hexanes, 1.0 ml, 1.38 mmol) and stirring was continued for 1 hour then warmed to 0°C. Anhydrous zinc bromide (310 mg, 1.38 mmol) was added and the resulting solution stirred at room temperature for 1 hour. A solution of *N*-Boc-L-alaninal **53** (100 mg, 0.58 mmol) in THF (2 ml) was added to the above solution at -78°C, then stirred for a further 24 hours at room temperature whereafter sat. aq. NH_4Cl (5ml) was added and the layers separated. The aqueous layer was extracted with ether (2 x 5 ml), the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography of the residue (hexane-EtOAc 6:1) gave the recovered acetylene **117** (223 mg) and the *β-amino alcohols* **118a/b** (41 mg, 18%).

N.B. The ratio of diastereomers **118a** and **118b** was determined by HPLC analysis using a Baker Chiralcel OD (4.6 x 250) column and detected by a Waters 486 tunable absorbance detector (λ 254 nm). The column was eluted with 95:5 hexane/IPA at a flow rate of 0.2 ml/min. The diastereomers were not separated due to dificulites in finding an appropriate chromatography solvent system, hence the nmr data given below, results from peak selection.

(2*S*, 3*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-7-benzyloxy-6,6-ethylenedioxy-3-hydroxy hept-4-yne **118a**: R_F (hexane-EtOAc 1:1) 0.42; υ_{max}/cm^{-1} (film, IR card) 3124-3586 (OH), 1705 (C=O), 1365 (CMe_3), 1165 (C-O); δ_H (250 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.5, CH*Me*), 1.41 (9H, s, $OCMe_3$), 3.4-3.5 (1H, br.s, CHO*H*), 3.66 (2H, s, CH_2OBn), 3.78-3.98 (1H, br.m, C*H*Me), 3.99-4.11 (4H, m, CH_2CH_2), 4.36 (1H, t, *J* 5.0, C*H*OH), 4.66 (2H, s, CH_2Ph), 4.80 (1H, br.d, *J* 8.5, N*H*) and 7.25-7.33 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 15.8 (CH_3, CH*Me*), 28.2 (CH_3, $OCMe_3$), 50.4 (CH, *C*HMe), 65.0 (CH_2, CH_2CH_2), 65.4 (CH, *C*HOH), 72.9, 73.7 (2xCH_2, CH_2Ph and CH_2OBn), 79.6, 81.9, 83.6 (C, 2x*C*-acetylene and O*C*Me$_3$), 127.5, 127.6, 128.2

(CH, *Ph*), 137.6 (C, *Ph*) and 155.6 (C, *C*=O); *m/z* (F.A.B.) 392 [$(MH)^+$, 4.7%], 391 (34), 334 (6), 57 (86); [Found; $(MH)^+$, 392.20689. $C_{21}H_{30}NO_6$ requires MH, 392.20731].

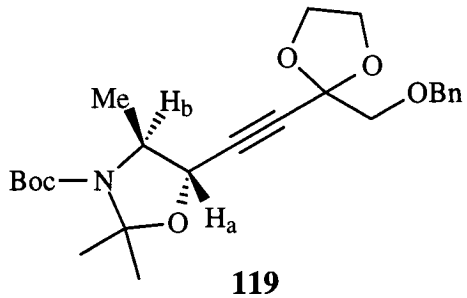
5.3.12 (4S, 5SR)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[4-benzyloxy-3, 3-ethylenedioxybut-1-yn-1-yl]oxazolidine ***119/120***



118a/b **119/120**

To a stirred solution of the β-amino alcohol **118a/b** (165 mg, 0.42 mmol) in DCM (5 ml) was added 2,2-dimethoxypropane (5 ml) and a catalytic amount of *para*-toluenesulfonic acid and the solution heated under reflux for 2 hours. Water (10 ml) was added, the phases separated and the organic fraction washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with hexane-ethyl acetate (5:1) gave the *oxazolidine derivative* **119/120** as an oil (144 mg, 80%).

N.B. The ratio of the diastereomers was determined by HPLC analysis using a Baker Chiralcel OD (4.6 x 250) column and detected by a Waters 486 tunable absorbance detector (λ 254 nm). The column was eluted with 90:10 hexane/IPA at a flow rate of 0.5 ml/min. The relevant data for the minor diastereomer **120** was unobtainable due to insufficient quantites isolated



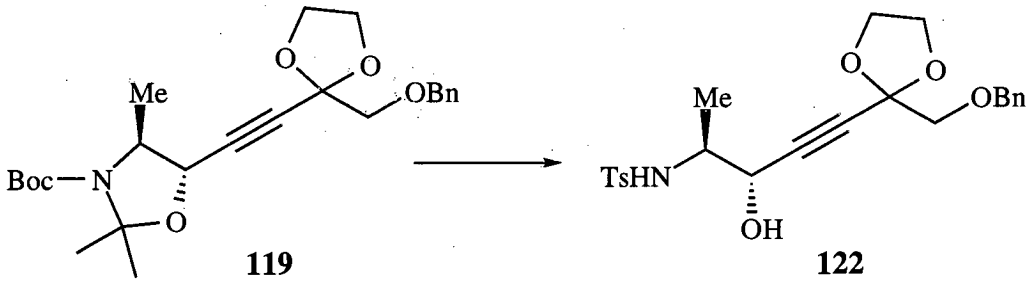
119

(4*S*, 5*S*)-*N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-methyl-5-[4-benzyloxy-3,3-ethylene dioxybut-1-yn-1-yl]oxazolidine **119** R_F 0.31; υ_{max}/cm^{-1} (film, IR card) 1696 (C=O), 1383 (CMe_2), 1109, 1085 (C-O); δ_H (250 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5, CH*Me*), 1.46 (9H, s, OC*Me*$_3$), 1.51, 1.67 (6H, 2xs, *Me*-oxazolidine), 3.67 (2H, s, CH_2OBn), 4.01-4.10 (5H, m, CH_2CH_2 and C*H*Me), 4.42 (1H, d, *J* 3.0, C*H*CHMe), 4.66 (2H, s, CH_2Ph) and 7.24-7.34 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 19.3 (CH_3, CH*Me*), 27.7 (brCH_3, 2x*Me*-oxazolidine), 28.3 (CH_3, OC*Me*$_3$), 59.3 (CH, *C*HMe), 65.2 (CH_2, CH_2CH_2), 70.4 (CH, *C*H-O), 72.8, 73.8 (2xCH_2, CH_2Ph and CH_2OBn), 79.9, 82.3, 83.4 (3xC, 2x*C*-acetylene and O*C*Me$_3$), 95.8 (C, *C*-oxazolidine), 101.8 (C, *C*-ketal), 127.5, 127.6, 128.2 (CH, *Ph*), 137.7 (C, *Ph*) and 151.5 (C, *C*=O); *m/z* (F.A.B.) 432 [$(MH)^+$, 9.4%], 430 (10), 416 (4), 91 (90), 57 (100); [Found: $(MH)^+$, 432.23685. $C_{24}H_{33}NO_6$ requires MH, 432.23861].

nOe data:-

Irradiated Proton	Enhancement Observed (%)
H_a	H_b (3%); Me (2%)
H_b	Me (1%)
Me	H_a (3%); H_b (15%)

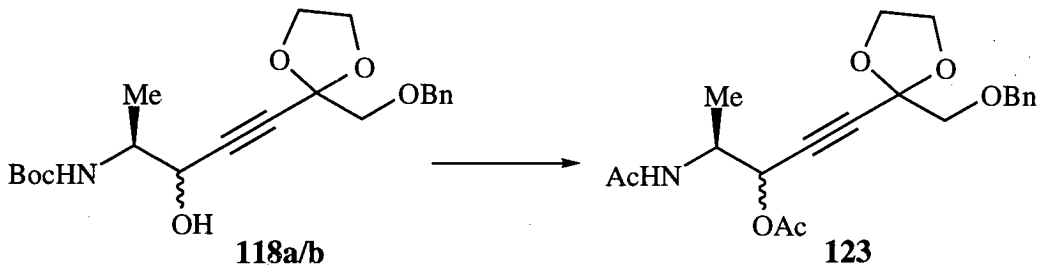
5.3.13 (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-7-benzyloxy-6,6-ethylenedi oxy-3-hydroxyhept-4-yne ***122***



The oxazolidine **119** (28 mg, 0.07 mmol) was treated with trifluoroacetic acid (99%, 1 ml) at room temperature for 30 minutes and then concentrated *in vacuo*. The residue was suspended in DCM (1 ml) and 1,4-dioxane (1 ml) and cooled to 0°C before addition of triethylamine (36 µl, 0.26 mmol) and tosyl chloride (13 mg, 0.07 mmol)

and the mixture stirred for 30 minutes at 0°C then at room temperature for a further 24 hours. Water (5 ml) and EtOAc (5 ml) were added, the layers separated and the organic fraction washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with hexane-EtOAc (1:1) gave the *N-Tosyl amide* **122** as an oily residue (9 mg, 32%). R_F 0.39; υ_{max}/cm^{-1} (film, IR card) 3470br (OH), 1332, 1162 (SO_2-N), 1094 (C-O); δ_H (250 MHz, DMSO) 1.75 (3H, d, *J* 6.5, CH*Me*), 2.38 (3H, s, *Me*-aryl), 3.05-3.10 (1H, br.m, C*H*Me), 3.64 (2H, s, CH_2OBn), 3.95-4.00 (4H, m, CH_2CH_2), 4.26 (1H, t, *J* 5.0, C*H*OH), 4.61 (2H, s, CH_2Ph), 5.68 (1H, d, *J* 5.0, O*H*), 7.28-7.39 (7H, m, *Ph* and *aryl*), 7.63 (1H, d, *J* 7.0, N*H*) and 7.71 (2H, d, *J* 8.0, *aryl*); δ_C (62.9 MHz, DMSO) 14.5 (CH_3, CH*Me*), 21.1 (CH_3, *Me*-aryl), 53.0 (CH, *C*HMe), 64.8, 64.9 (CH_2 and CH, CH_2CH_2 and *C*HOH), 72.8, 73.0 (2xCH_2, CH_2Ph and CH_2OBn), 81.7, 83.7 (2xC, *C*-acetylene), 101.6 (C, *C*-ketal), 126.6, 127.6, 128.3, 129.7 (CH, *Ph* and *aryl*), 138.3, 138.5 (C, *Ph* and *aryl*) and 142.6 (C, *aryl*); *m/z* (F.A.B.) 446 [$(MH)^+$, 3.5%], 198 (35), 155 (52), 91 (63), 57 (100); [Found: $(MH)^+$, 446.16379. $C_{23}H_{28}NO_6S$ requires MH, 446.16374].

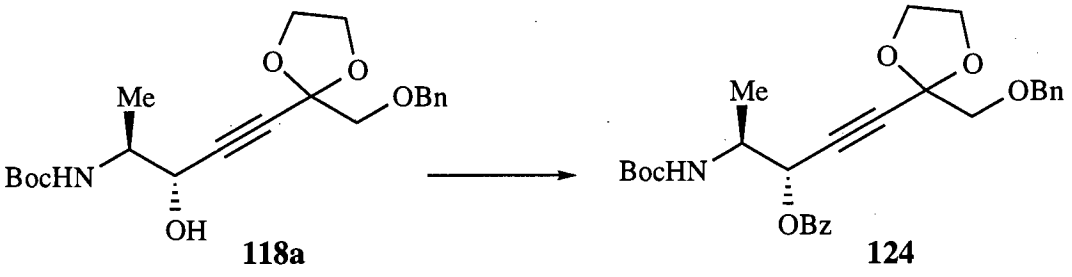
5.3.14 (2S, 3SR)-2-acetamido-3-acetyloxy-7-benzyloxy-6,6-ethylenedioxy-hept-4-yne ***123***



The β-amino alcohol **118a/b** (60 mg, 0.15 mmol) was treated with trifluoroacetic acid (99%, 1 ml) at 0°C for 1 hour, whereafter water (1 ml) and DCM (1 ml) were added and the solvents removed under reduced pressure. The residue was taken up in DCM (5 ml), washed with sat. aq. $NaHCO_3$ (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A portion of this residue (18 mg) was taken up in anhydrous acetic anhydride (0.5 ml) and pyridine (0.5 ml) and stirred under a nitrogen atmosphere for 20 hours. After addition of dilute HCl (5 ml) and EtOAc (5 ml), the organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with EtOAc yielded the *N-acetyl amide* **123** as

an oil (10 mg, 18%). R_F 0.46; υ_{max}/cm^{-1} (film, IR card) 1739 (C=O, ester), 1657 (C=O, amide), 1373 (CMe_3), 1224 and 1027 (C-O); δ_H (250 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5, CH*Me*), 1.85, 2.07 (6H, s, 2x*Me*CO), 3.68 (2H, s, CH_2OBn), 3.70-4.09 (4H, m, CH_2CH_2), 4.3-4.5 (1H, br.m, C*H*Me), 4.67 (2H, s, CH_2Ph), 5.39-5.41 (1H, m, C*H*OAc diastereomers), 5.60 (1H, br.d, N*H* diastereomers) and 7.25-7.35 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 15.9 (CH_3, CH*Me*), 20.6, 23.0 (2xCH_3, *Me*CO), 46.7 (CH, *C*HMe), 65.2 (CH_2, CH_2CH_2), 66.5 (CH, *C*HOAc), 73.2, 73.8 (2xCH_2, CH_2Ph and CH_2OBn), 79.3, 79.7, 82.8 (3xC, 2x*C*-acetylene and O*C*Me_3), 101.8 (C, *C*-ketal), 127.7, 127.8 (CH, *Ph*), 128.3 (C, *Ph*), 169.3 and 169.6 (2xC, *C*=O); *m/z* (F.A.B.) 376 [$(MH)^+$, 100%], 332 (7), 91 (30), 86 (48), 43 (37); [Found: $(MH)^+$, 376.17765. $C_{20}H_{26}NO_6$ requires 376.17601]. N.B The precursor amino alcohol **118** used for this reaction was of low diastereomeric ratio hence the acetylated compound **123** contained both diastereomers.

*5.3.15 (2S, 3S)-*N*-(tert-butoxycarbonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6,6-ethylenedioxyhept-4-yne* ***124***

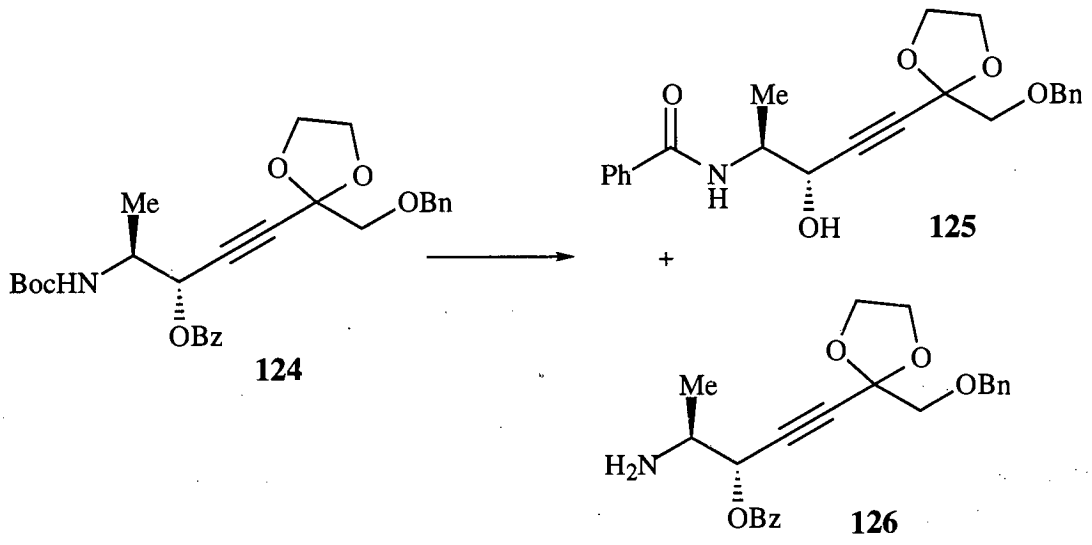


118a **124**

Triethylamine (190 µl, 1.35 mmol) was added dropwise to an ice cold stirred solution of the β-amino alcohol **118a** (427 mg, 1.09 mmol) in DCM (10 ml) under an argon atmosphere and stirring was continued for 10 minutes. Benzoyl chloride (152 µl, 1.30 mmol) was added slowly and the mixture stirred for a further 30 minutes at 0°C then at room temperature for 12 hours. The solvent was removed *in vacuo* and the resultant oily residue subjected to column chromatography eluting with hexane-EtOAc (2:1) to give the *benzoate ester* **124** (491 mg, 90%) as an oil. R_F 0.50; (Found: C, 67.61; H, 6.77; N, 2.66; $C_{28}H_{33}NO_7$ requires C, 67.86; H, 6.71; N, 2.83%); υ_{max}/cm^{-1} (film, IR card) 1710br (C=O), 1518 (aryl), 1258, 1107 (C-O); δ_H (250 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5, CH*Me*), 1.37 (9H, s, O*C*Me_3), 3.69 (3H, s, CH_2OBn and N*H*), 4.00-4.12 (10H, m, CH_2CH_2 and C*H*Me), 4.68 (2H, s, CH_2Ph), 5.46 (1H, br.m, C*H*OBz) and 7.24-8.04 (5H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 16.4 (CH_3, CH*Me*), 28.1 (CH_3,

$OCMe_3$), 48.4 (CH, *C*HMe), 65.1 (CH_2, CH_2CH_2), 66.4 (CH, *C*HOBz), 72.8, 73.7 (2xCH_2, CH_2Ph and CH_2OBn), 79.5, 79.8, 83.0 (3xC, 2x*C*-acetylene and $OCMe_3$), 101.7 (C, *C*-ketal), 127.5, 128.2, 129.8, 133.2 (CH, *Ph*), 129.2, 137.6 (2xC, *Ph*), 154.7 (C, *C*=O urethane) and 164.9 (C, *C*=O benzoate); *m/z* (F.A.B.) 496 [$(MH)^+$, 1.1%], 318 (10), 274 (11), 57 (100); [Found; $(MH)^+$, 496.23250. $C_{28}H_{34}NO_7$ requires MH, 496.23353].

5.3.16 Attempted preparation of (2S, 3S)-2-amino-3-benzoyloxy-7-benzyloxy-6,6-ethylenedioxyhept-4-yne ***126***



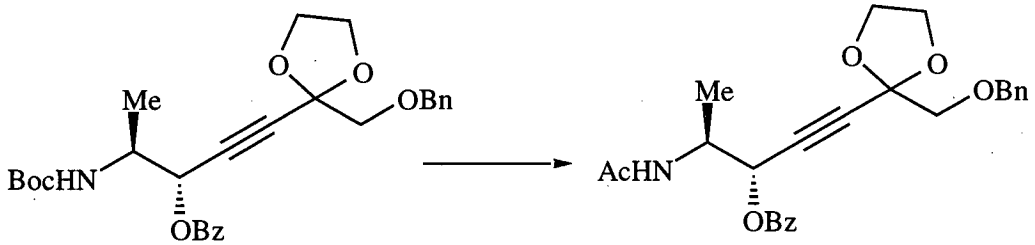
A solution of the benzoyl ester **124** (55 mg, 0.11 mmol) in DCM (1 ml) was treated with trifluoroacetic acid (99%, 1 ml) at room temperature and stirred for 1 hour. Water (2 ml) and DCM (2 ml) were added and the organic liquors washed with sat. aq. $NaHCO_3$ (5 ml), brine (5 ml) and dried over anhydrous Na_2SO_4. Column chromatography of the residue eluting with EtOAc-MeOH (20:1) gave two separate products, the benzoyl amide **125** and the *amine* **126**.

(2*S*, 3*S*)-2-benzamido-7-benzyloxy-6,6-ethylenedioxy-3-hydroxy-hept-4-yne **125**: R_F (hexane-EtOAc 2:1) 0.36; υ_{max}/cm^{-1} (film, IR card) 3345br (OH), 1638 (C=O), 1538 (aryl), 1104 (C-O); δ_H (250 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.5, CH*Me*), 1.60-2.00 (1H, br.s, O*H*), 3.65 (2H, s, CH_2OBn), 3.93-4.07 (4H, m, CH_2CH_2), 4.32-4.41 (1H, m, C*H*Me), 4.54 (1H, d, *J* 5.0, C*H*OH), 4.62 (2H, s, CH_2Ph), 6.41 (1H, d, *J* 8.5, N*H*), and 7.24-7.76 (10H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 15.6 (CH_3, CH*Me*), 49.7 (CH, *C*HMe), 65.1 (CH_2, CH_2CH_2), 73.1, 73.7, (2xCH_2, CH_2Ph and

CH_2OBn), 82.2, 83.5 (2xC, *C*-acetylene), 101.8 (C, *C*-ketal), 126.9, 127.0, 127.7, 128.3, 128.4, 131.5 (CH, *Ph*), 134.1, 137.5 (2xC, *Ph*) and 167.6 (C, *C*=O); *m/z* (F.A.B.) 396 [$(MH)^+$, 47.7%], 178 (10), 148 (40), 105 (100), 77 (29); [Found: $(MH)^+$, 396.18185. $C_{23}H_{26}NO_5$ requires MH, 396.18110].

(2*S*, 3*S*)-2-amino-3-benzoyloxy-7-benzyloxy-6,6-ethylenedioxyhept-4-yne **126**: R_F (EtOAc) 0.30; δ_H (250 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.5, CH*Me*), 3.63 (3H, br.s, C*H*$_2$OBn and C*H*Me), 3.90-4.08 (4H, m, C*H*$_2$C*H*$_2$), 4.62 (2H, s, C*H*$_2$Ph), 5.77 (1H, br.d, *J* 5.5, C*H*OBz) and 7.25-8.08 (12H, m, *Ph* and N*H*$_2$); δ_C (62.9 MHz, $CDCl_3$) 14.5 (CH_3, CH*Me*), 19.8 (CH, *C*HMe), 64.7 (CH, *C*HOBz), 65.2 (CH_2, *C*H_2CH_2), 72.9, 73.8 (2xCH_2, *C*H_2Ph and *C*H_2OBn), 77.7, 85.2 (2xC, *C*-acetylene), 101.5 (C, *C*-ketal), 127.8, 128.3, 129.9, 133.7 (CH, *Ph*) 137.2 (C, *Ph*) and 164.8 (C, *C*=O); *m/z* (F.A.B.) 396 [$(MH)^+$, 100%], 91 (22), 77 (31); [Found: $(MH)^+$, 396.18253. $C_{23}H_{26}NO_5$ requires MH, 396.18110].

5.3.17 (2S, 3S)-2-acetamido-3-benzoyloxy-7-benzyloxy-6,6-ethylenedioxyhept-4-yne ***127***

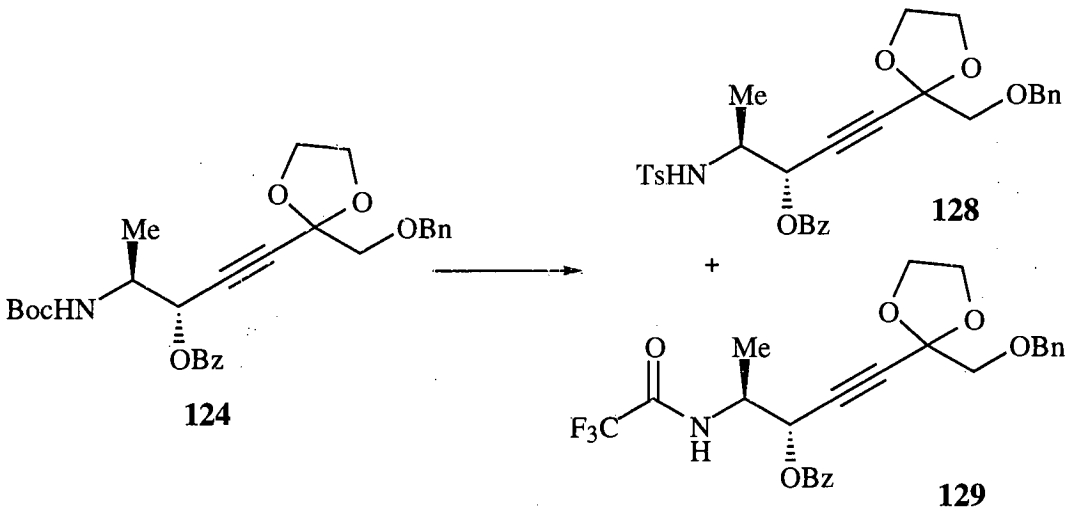


124 **127**

Trifluoroacetic acid (99%, 1 ml) was added dropwise to the benzoyl ester **124** (66 mg, 0.13 mmol) in DCM (0.5 ml) at 0°C and the mixture stirred for 1 hour at room temperature. Water (5 ml) and DCM (5 ml) were added and the organic layer washed with sat. aq. $NaHCO_3$ (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give an oil (64mg). The residue was taken up in pyridine (1 ml) and acetic anhydride (1 ml) and stirred for 15 hours under a nitrogen atmosphere. Dilute HCl (2 ml) and EtOAc (2 ml) were added and the organic phase dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatogrpahy (EtOAc) yielded the *N-acetamide* **127** (37 mg, 66%). R_F 0.42; υ_{max}/cm^{-1} (film, IR card) 1722 (C=O, benzoate), 1655 (C=O, acetate), 1265, 1103 (C-O); δ_H (250 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5 CH*Me*), 1.83 (3H, s, *Me*CO), 3.70 (2H, s, C*H*$_2$OBn),

3.97-4.12 (4H, m, CH_2CH_2), 4.43-4.51 (1H, m, CHMe), 4.67 (3H, s, CH_2Ph), 5.63 (1H, d, *J* 5.5, CHOBz), 5.70 (1H, br.d, *J* 9.0, NH) and 7.22-8.03 (10H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 16.0 (CH_3, CH*Me*), 23.0 (CH_3, *Me*CO), 46.8 (CH, CHMe), 65.1 (2xCH_2, CH_2CH_2), 65.8 (CH, CHCHMe), 73.2, 73.8 (2xCH_2, CH_2Ph and CH_2OBn), 79.8, 83.1 (2xC, *C*-acetylene), 101.8 (C, *C*-ketal), 127.7, 128.3, 129.7, 133.3 (CH, *Ph*), 129.1, 137.5 (C, *Ph*), 164.9 (C, *C*=O benzoate) and 169.4 (C, *C*=O acetate); *m/z* (F.A.B.) 438 [$(MH)^+$, 84.1%], 105 (83), 86 (46), 77 (23), 44 (100).

5.3.18 Attempted preparation of (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6,6-ethylenedioxyhept-4-yne ***128***



The benzoyl ester **124** (193 mg, 0.39 mmol) was treated with trifluoroacetic acid (99%, 3 ml) for 40 minutes at room temperature and then concentrated under reduced pressure. A cooled (0°C) stirred solution of the residue in DCM (2 ml) and 1,4-dioxane (2 ml) was treated with triethylamine (220 µl, 0.56 mmol) and tosyl chloride (81 mg, 0.43 mmol) and stirring continued for 30 minutes at low temperature and then at room temperature for 4 hours. Water (5 ml) and EtOAc (5 ml) were added and the organic layer washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated. Column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the trifluoroacetamide **129** (33 mg) and the *N-Tosyl amide* **128** (82 mg, 40%).

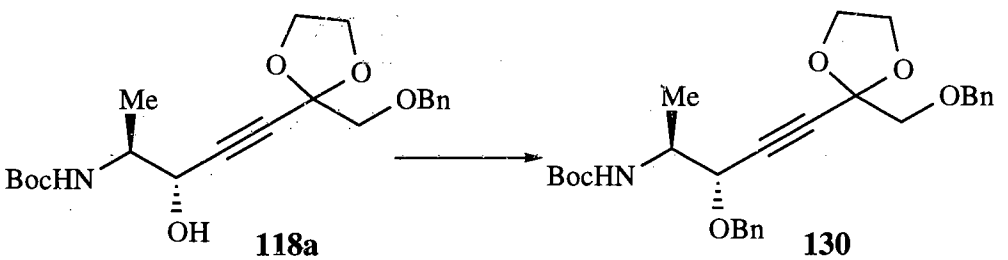
(2*S*, 3*S*)-3-benzoyloxy-7-benzyloxy-6,6-ethylenedioxy-2-trifluoroacetamidohept-4-yne **129**: R_F 0.33; υ_{max}/cm^{-1} (film, IR card) 1728 (C=O), 1265 (C-O), 1179 (C-F), 1095 (C-O); δ_H (250 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.5, CH*Me*), 3.68 (2H, s,

C*H*$_2$OBn), 4.01-4.11 (4H, m, C*H*$_2$C*H*$_2$), 4.50-4.54 (1H, m, C*H*Me), 4.67 (2H, s, C*H*$_2$Ph), 5.71 (1H, d, *J* 5.5, C*H*OBz), 6.66 (1H, br.d, *J* 9.0, N*H*) and 7.25-8.04 (10H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 15.8 (CH_3, CH*Me*), 48.1 (CH, *C*HMe), 65.1, 65.2 (CH_2 and CH, *C*H$_2$*C*H$_2$ and *C*HOBz), 72.9, 73.7 (2xCH_2, *C*H$_2$Ph and *C*H$_2$OBn), 78.7, 84.1 (2xC, *C*-acetylene), 101.7 (C, *C*-ketal), 117.8 (C, *C*F$_3$), 127.6, 127.8, 128.2, 128.4, 129.8, 133.5 (CH, *Ph*), 128.6, 137.5 (C, *Ph*), 156.3 (C, *C*=O amide) and 164.9 (C, *C*=O ester); δ_F (235 MHz, $CDCl_3$) -76.2 (F, C*F*$_3$); *m/z* (F.A.B.) 492 [$(MH)^+$, 0.6%], 370 (5), 193 (7), 105 (100), 91 (78); [Found: $(MH)^+$, 492.16485. $C_{25}H_{25}NO_6F_3$ requires MH, 492.16340].

(2*S*, 3*S*)-*N*-(4-methylphenylsulfonyl)-2-amino-3-benzoyl-7-benzyl-6,6-ethylenedioxy hept-4-yne **128**: R_F 0.20; υ_{max}/cm^{-1} (film, IR card) 1726 (C=O), 1261 (C-O), 1162 (SO_2-N), 1093 (C-O); δ_H (250 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.5, CH*Me*), 2.36 (3H, s, *Me*-aryl), 3.67 (2H, s, C*H*$_2$OBn), 3.67-3.90 (1H, br.m, C*H*Me), 4.00-4.09 (4H, m, C*H*$_2$C*H*$_2$), 4.69 (2H, s, C*H*$_2$Ph), 4.98 (1H, d, *J* 9.5, N*H*), 5.56 (1H, d, *J* 6.0, C*H*OBz), and 7.18-7.95 (14H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 16.9 (CH_3, CH*Me*), 21.3 (CH_3, *Me*-aryl), 51.2 (CH, *C*HMe), 65.1 (CH_2, *C*H$_2$*C*H$_2$), 66.1 (CH, *C*HOBz), 72.9, 73.7 (2xCH_2, *C*H$_2$Ph and *C*H$_2$OBn), 79.0, 83.9 (2xC, *C*-acetylene), 101.7 (C, *C*-ketal), 126.8, 127.6, 129.5, 129.7, 133.3, 137.8 (CH, *Ph* and *aryl*), 128.9, 143.2 (C, *Ph* and *aryl*) and 164.7 (C, *C*=O); *m/z* (C.I.) 567 [$(M+NH_4)^+$], 198, 193, 91; [Found: $(M+NH_4)^+$, 567.21650. $C_{30}H_{35}N_2O_7S$ requires $(M+NH_4)$, 567.21649].

5.3.19 Attempted benzylation to give (2S, 3S)-N-(tert-butoxycarbonyl)-2-amino-3,7-dibenzyloxy-6,6-ethylenedioxyhept-4-yne ***130***

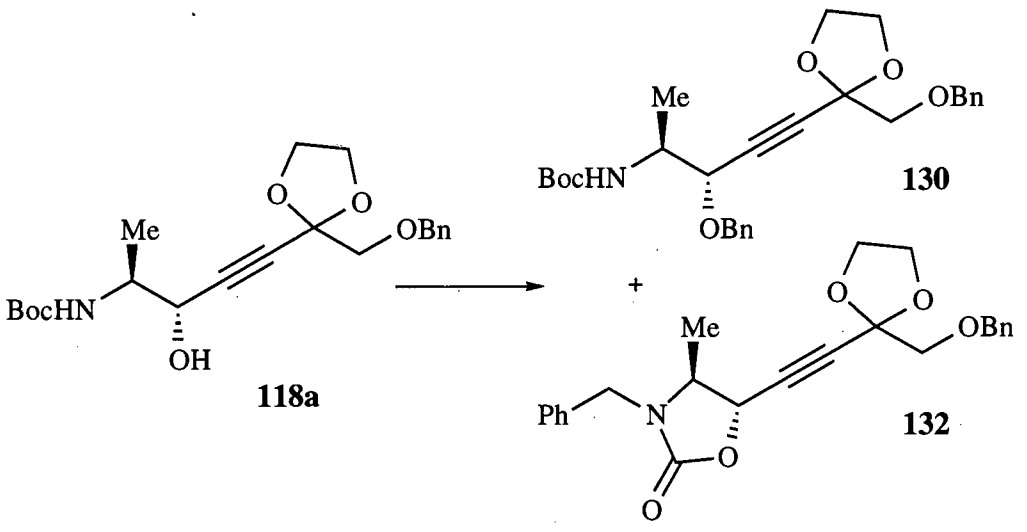
Method 1, BnBr, Ag_2O, ether:-



To a solution of β-amino alcohol **118a** (74 mg, 0.19 mmol) in ether (4 ml) was added silver (I) oxide (48 mg, 0.20 mmol) and benzyl bromide (30 μl, 0.25 mmol) and the black suspension heated under reflux for 10 hours. The reaction mixture was filtered

through a plug of Celite, washed with ether (2 x 5 ml), and the combined organic liquors dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the *benzyl ether* **130** (7 mg, 8%) and unreacted β-amino alcohol **118a** (68 mg, 92%).

Method 2, BnBr, NaH, DMF:-



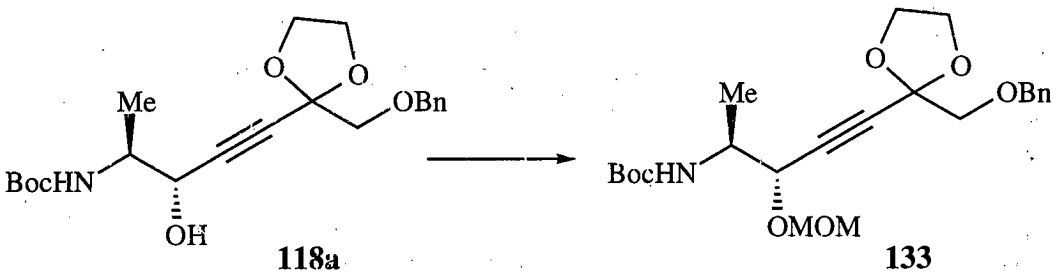
Sodium hydride (60% dispersion in oil, 7 mg, 0.18 mmol) was added to a stirred solution of the β-amino alcohol **118a** (52 mg, 0.13 mmol) in DMF (3 ml) at 0°C and stirring continued for 30 minutes under a nitrogen atmosphere. Benzyl bromide (19 μl, 0.16 mmol) was added dropwise and the reaction stirred at room temperature for 18 hours. Water (5 ml) and ether (5 ml) were added and the combined organic fraction washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the *benzyl ether* **130** (11 mg, 17%) and the oxazolidinone **132** (48 mg).

(2*S*, 3*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-3,7-dibenzyloxy-6,6-ethylenedioxyhept-4-yne **130**: R_F 0.48; υ_{max}/cm^{-1} (film, IR card) 1713 (C=O), 1498 (aryl), 1058, 1106 (C-O); δ_H (250 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5, CH*Me*), 1.42 (9H, s, OC*Me*$_3$), 3.71 (2H, s, CH_2OBn), 3.90-4.11 (5H, m, CH_2CH_2 and C*H*Me), 4.19 (1H, d, *J* 4.0, C*H*OBn), 4.47 (1H, d, *J* 11.5, CHOCH_2Ph), 4.70 (2H, s, CH_2OCH_2Ph), 4.75 (1H, d, *J* 11.5, CHOCH_2Ph) and 7.25-7.35 (10H, m, *Ph*); δ_C (62.9 MHz, $CDCl_3$) 16.3 (CH_3, CH*Me*), 28.2 (CH_3, OC*Me*$_3$), 48.8 (CH, *C*HMe), 65.0 (CH_2, CH_2CH_2), 70.8 (CH_2, *C*H_2Ph), 71.3 (CH, *C*HOBn), 73.0, 73.7 (2xCH_2, *C*H_2Ph and *C*H_2OBn), 79.2, 81.4, 83.4 (3xC, 2x*C*-acetylene and O*C*Me$_3$), 101.8 (C, *C*-ketal), 127.5, 127.6, 127.7, 128.2 (CH, *Ph*), 137.3, 137.7 (2xC, *Ph*) and 155.0 (C, *C*=O); *m/z*

(F.A.B.) 482 [$(MH)^+$, 1.8%], 91 (100), 59 (82); [Found: $(MH)^+$, 482.25493. $C_{28}H_{36}NO_6$ requires MH, 482.25426].

(4S, 5S)-*N*-benzyl-4-methyl-5-[4-benzyloxy-3,3-ethylenedioxybut-1-yn-1-yl]oxazolidin-2-one **132**: R_F (DCM) 0.2; υ_{max}/cm^{-1} (film, IR card) 1759 (C=O), 1105, 1027 (C-O); δ_H (250 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.0, CH*Me*), 3.57-3.68 (3H, m, CH_2OBn and C*H*Me), 4.03-4.13 (5H, m, CH_2CH_2 and C*H*-O), 4.60-4.77 (4H, m, OCH_2Ph and NCH_2Ph) and 7.25-7.30 (10H, m, OCH_2*Ph* and NCH_2*Ph*); δ_C (62.9 MHz, $CDCl_3$) 17.0 (CH_3, CH*Me*), 45.8 (CH_2, NCH_2Ph), 57.0 (CH, *C*HMe), 65.2 (CH_2, CH_2CH_2), 69.5 (CH, *C*H-O), 72.6, 73.7 (2xCH_2, OCH_2Ph and CH_2OBn), 79.3, 84.4 (2xC, *C*-acetylene), 101.7 (C, *C*-ketal), 127.5, 127.8, 128.2, 128.7 (CH, *Ph*), 127.6, 135.3 (C, *Ph*) and 155.6 (C, *C*=O); *m/z* (F.A.B.) 408 [$(MH)^+$, 100%], 318 (8), 300 (1), 91 (27); [Found: $(MH)^+$, 408.18159. $C_{24}H_{26}NO_5$ requires MH, 408.18110].

5.3.20 (2S, 3S)-N-(tert-butoxycarbonyl)-2-amino-7-benzyloxy-6,6-ethylenedioxy-3-methoxymethyloxyhept-4-yne ***133***

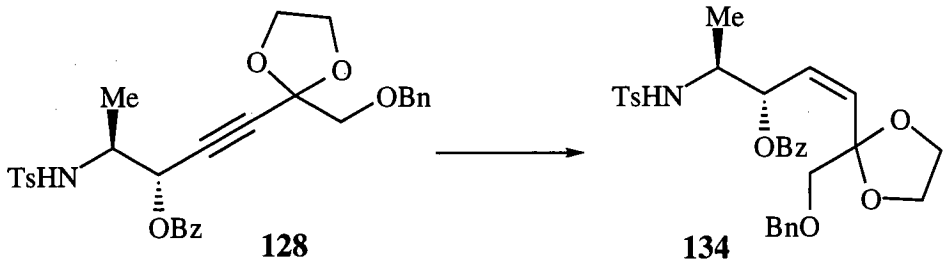


118a **133**

Dimethoxymethane (2 ml) and phosphorous pentoxide (670 mg) were added to a solution of the β-amino alcohol **118a** (90 mg, 0.23 mmol) in $CHCl_3$ (3 ml) and the mixture stirred for 30 minutes under an atmosphere of nitrogen. The reaction mixture was poured into ice cold sat. aq. $NaHCO_3$ (3 ml), the aqueous layer extracted with EtOAc (2 x 5 ml) and the combined organic liqours were washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the *MOM ether* **133** as an oil (55 mg, 55%). R_F 0.28; υ_{max}/cm^{-1} (film, IR card) 1712 (C=O), 1366 (CMe_3), 1163, 1032 (C-O); δ_H (250 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5, CH*Me*), 1.41 (9H, s, $OCMe_3$), 3.35 (3H, s, CH_2OMe), 3.67 (2H, s, CH_2OBn), 3.8-4.11 (5H, br.m, CH_2CH_2 and C*H*Me), 4.41 (1H, d, *J* 4.0, C*H*OMOM), 4.56 (1H, d, *J* 6.5, CH_2OMe), 4.67 (2H, s, CH_2Ph), 4.85 (1H, d, *J* 6.5, CH_2OMe) and 7.25-7.34 (5H, m, *Ph*); δ_C (62.9 MHz,

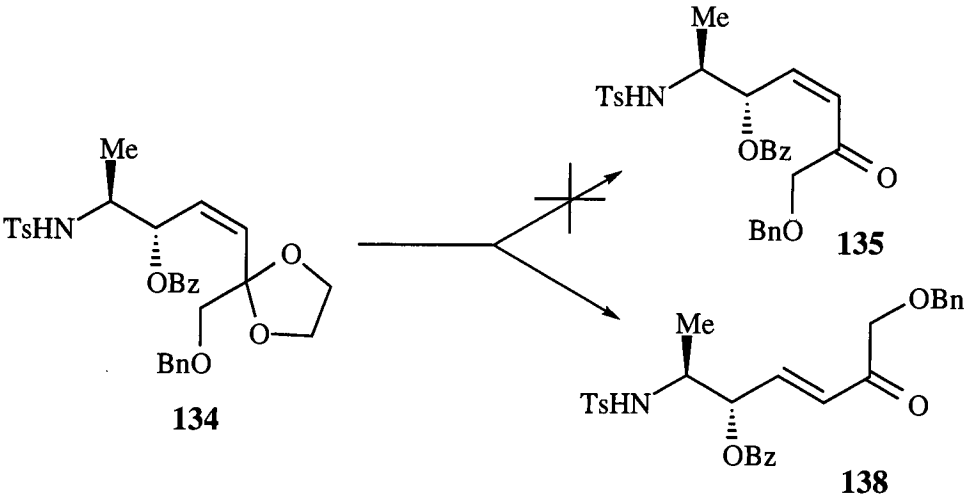
$CDCl_3$) 16.1 (CH_3, CH*Me*), 28.2 (CH_3, OC*Me*$_3$), 48.7 (CH, *C*HMe), 55.6 (CH_3, CH_2O*Me*), 65.0 (CH_2, *C*H_2*C*H_2), 68.2 (CH, *C*HOMOM), 72.9, 73.7 (2xCH_2, *C*H_2Ph and *C*H_2OBn), 79.3, 80.0, 82.9 (3xC, 2x*C*-acetylene and O*C*Me$_3$), 94.3 (CH_2, *C*H_2OMe), 101.8 (C, *C*-ketal), 127.5, 127.6, 128.2 (CH, *Ph*), 137.7 (C, *Ph*) and 154.5 (C, *C*=O); *m/z* (F.A.B.) 436 [(MH)$^+$, 5.2%], 193 (43), 91 (73), 57 (100), 45 (63); [Found: (MH)$^+$, 436.23504. $C_{23}H_{34}NO_4$ requires MH, 436.25353].

5.3.21 (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6, 6-ethylenedioxy-(Z)-hept-4-ene ***134***



To a stirred solution of the acetylene **128** (43 mg, 0.08 mmol) in EtOAc-hexane (2:1, 3 ml) was added Lindlar catalyst (5% palladium on $CaCO_3$, 30 mg) and the deoxygenated mixture stirred for 17 hours under an atmosphere of hydrogen. The catalyst was removed by filtration through a plug of Celite and washed with EtOAc (2 x 2 ml) before concentration of the combined filtrates *in vacuo*. Column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the *Z-alkene* **134** (28 mg, 68%) and recovered acetylene **128** (8 mg). R_F 0.20; υ_{max}/cm^{-1} (film, IR card) 1719 (C=O), 1327 (SO_2), 1266 (C-O), 1162 (SO_2-N) 1094 (C-O); δ_H (250 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.5, CH*Me*), 2.34 (3H, s, *Me*-aryl), 3.58 (2H, s, C*H*$_2$OBn), 3.58-3.67 (1H, m, C*H*Me), 3.94-4.01 (4H, m, C*H*$_2$C*H*$_2$), 4.60 (1H, d, *J* 12.0, C*H*$_2$Ph), 4.67 (1H, d, *J* 12.0, C*H*$_2$Ph), 5.49-5.61 (3H, m, C*H*OBz, N*H* and C*H*CHCHOBz), 6.08 (1H, dd, *J* 8.0, 4.0, C*H*CHOBz) and 7.15-7.96 (14H, m, *Ph* and *aryl*); δ_C (62.9 MHz, $CDCl_3$) 18.5 (CH_3, CH*Me*), 21.3 (CH_3, *Me*-aryl), 53.2 (CH, *C*HMe), 65.0 (CH_2, *C*H_2*C*H_2), 72.4 (CH, *C*HOBz), 72.7, 73.6 (2xCH_2, *C*H_2Ph and *C*H_2OBn), 108.0 (C, *C*-ketal), 126.9, 127.5, 127.6, 127.7, 128.8, 129.3, 129.5 (CH, *Ph* and *aryl*), 132.5, 132.9, 133.0 (3xCH, 2x*C*H-alkene and *Ph*), 137.8, 138.0 (C, *Ph* and *aryl*) and 165.3 (*C*=O); *m/z* (C.I.) 569 [(M+NH_4)$^+$]; [Found: (M+NH_4)$^+$, 569.23200. $C_{30}H_{37}N_2O_7S$ requires (M+NH_4), 569.23215].

5.3.22 Attempted preparation of (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6-oxo-(Z)-hept-4-ene ***135***



Method 1. Use of PPh_3 and CBr_4:-

A solution of triphenylphosphine (16 mg, 0.06 mmol) in DCM (0.5 ml) was added dropwise to an ice cold stirred solution of the 1,3-dioxolane **134** (17 mg, 0.03 mmol) and carbon tetrabromide (20 mg, 0.06 mmol) in DCM (1 ml) under an atmosphere of argon. The mixture was stirred for 30 minutes at 0°C then allowed to warm to room temperature for 2 hours. The mixture was filtered through a pad of silica, concentrated *in vacuo* and subjected to column chromatogaphy eluting with hexane-EtOAc (2:1) to give the *E*-alkene, (2*S*, 3*S*)-*N*-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6-oxo-(*E*)-hept-4-ene **138** (6 mg, 20%). R_F 0.22; υ_{max}/cm^{-1} (film, IR card) 1723br (C=O), 1268, 1093 (C-O); δ_H (360 MHz, $CDCl_3$) 1.15 (3H, *J* 6.5, CH*Me*), 2.37 (3H, s, *Me*-aryl), 3.68-3.72 (1H, m, C*H*Me), 4.16 (2H, s, CH_2OBn), 4.56 (2H, ov.d, *J* 1.0, CH_2Ph), 4.65 (1H, d, *J* 8.0, N*H*), 5.60 (1H, ov.ddd, *J* 5.0, 5.0, 1.5, C*H*OBz), 6.42 (1H, dd, *J* 16.0, 1.5, C*H*COCH$_2$), 6.77 (1H, dd, *J* 16.0, 5.0, C*H*CHOBz) and 7.42-7.98 (14H, m, *Ph* and *aryl*); δ_C (90.6 MHz, $CDCl_3$) 18.4 (CH_3, CH*Me*), 21.4 (CH_3, *Me*-aryl), 52.0 (CH, *C*HMe), 73.3, 74.2 (2xCH_2, CH_2Ph and CH_2OBn), 74.8 (CH, *C*HOBz), 124.9, 126.9, 127.8, 128.4, 128.5, 128.9, 129.7 (CH, *Ph* and *aryl*), 127.3, 127.9 (2xCH, *C*H-alkene), 136.9, 137.3, 143.6 (C, *Ph* and *aryl*) and 165.0 (C, *C*=O benzoate); *m/z* (C.I.) 525 [(M+NH_4)$^+$], 198, 105, 91; [Found: (M+NH_4)$^+$, 525.20600. $C_{28}H_{33}N_2O_6S$ requires (M+NH_4), 525.20593].

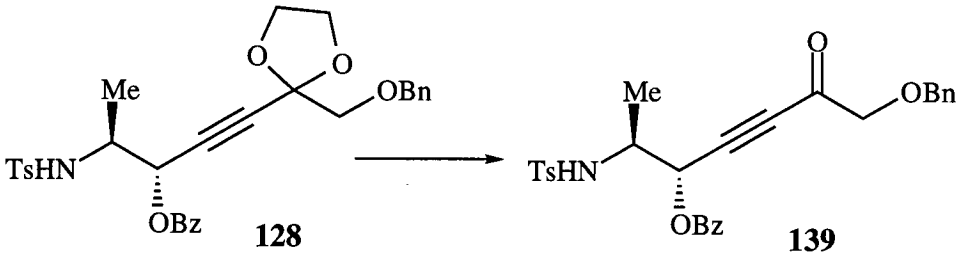
Method 2. Use of Acetic acid:-

The 1,3-dioxolane **134** (11 mg, 0.02 mmol) was treated with 80% acetic acid (2.5 ml) at 65°C for 18 hours. The reaction was quenched by careful addition to ice cold sat. aq. $NaHCO_3$ (20 ml) and extracted with ether (2 x 20 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and subjected to column chromatography eluting with hexane-EtOAc (2:1) to give the *E*-alkene **138** (5 mg, 51%).

Method 3. Use of Montmorrillonite K10:-

A stirred solution of the 1,3-dioxolane **133** (28 mg, 0.05 mmol) in DCM (1 ml) was treated with montmorillonite K10 (150 mg) and the mixture heated under reflux for 24 hours. The mixture was cooled to room temperature, filtered through a plug of Celite and concentrated under reduced pressure. Column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the *E*-alkene **138** (12 mg, 48%).

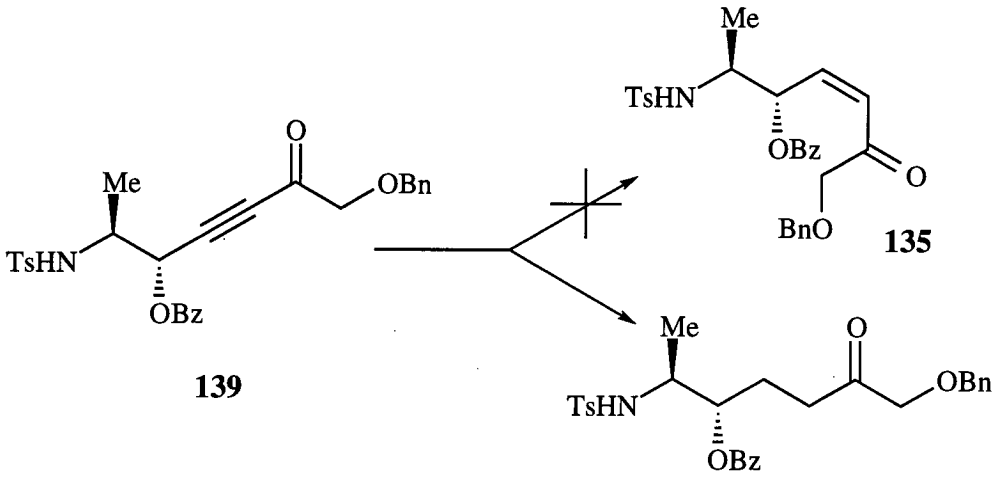
5.3.23 (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6-oxohept-4-yne ***139***



A stirred solution of the α,β-acetylenic ketal **128** (45 mg, 0.08 mmol) in DCM (1.5 ml) was treated with montmorrillonite K10 (200 mg) and the mixture was heated under reflux for 18 hours. The cooled mixture was filtered through a plug of Celite to remove the clay and the Celite washed with DCM (2 x 4 ml). Removal of the solvent under reduced pressure followed by column chromatography of the residue eluting with hexane-EtOAc (2:1) gave the *α,β-acetylenic ketone* **139** (16 mg, 40%). R_F 0.30; υ_{max}/cm^{-1} (film, IR card) 1728 (C=O ester), 1698 (C=O ketone), 1338, 1164 (SO_2-N), 1271, 1092 (C-O); δ_H (250 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.5, CH*Me*), 2.38 (3H, s, *Me*-aryl), 3:79-3.87 (1H, br.m, C*H*Me), 4.15 (2H, s, CH_2OBn), 4.62 (2H, s, CH_2Ph), 5.00 (1H, d, *J* 9.0, N*H*), 5.68 (1H, d, *J* 5.5, C*H*OBz) and 7.22-7.97 (14H, m, *Ph* and *aryl*); δ_C (62.9 MHz, $CDCl_3$) 17.2 (CH_3, CH*Me*), 21.4 (CH_3, *Me*-aryl),

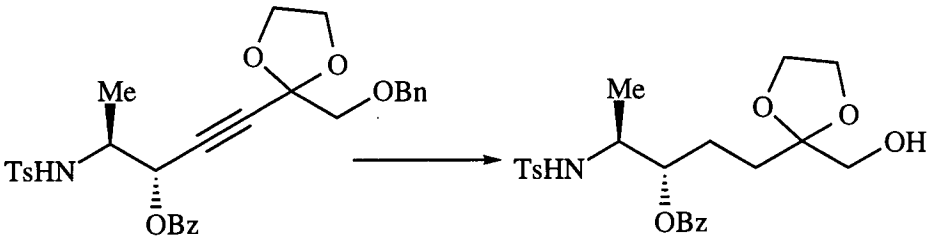
51.1 (CH, *C*HMe), 66.1 (CH, *C*HOBz), 73.4, 75.4 (2xCH_2, *C*H_2Ph and *C*H_2OBn), 82.9, 88.1 (2xC, *C*-acetylene), 126.8, 127.9, 128.0, 128.4, 129.7, 133.6 (CH, *Ph* and *aryl*), 128.3, 136.5, 137.4, 143.7 (C, *Ph* and *aryl*), 164.5 (C, *C*=O ester) and 183.9 (C, *C*=O ketone).

5.3.24 Attempted Lindlar catalysed hydrogenation to yield (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-7-benzyloxy-6-oxo-(E)-hept-4-ene ***135***



A solution of α,β-acetylenic ketone **139** (15 mg, 0.03 mmol) in EtOAc-hexane (3 ml, 2:1) was treated with the Lindlar catalyst (Pd on $CaCO_3$, 20mg). The flask was evacuated several times and the mixture stirred under an atmosphere of hydrogen for 18 hours. The mixture was filtered through a plug of Celite to remove the catalyst and washed with EtOAc (2 x 2 ml). The combined organic extracts were concentrated *in vacuo* and the residue subjected to column chromatography eluting with EtOAc-hexane (2:1) to give the fully saturated derivative **140** (15 mg, quantitative) as an oily residue. R_F 0.26; υ_{max}/cm^{-1} (film, IR card) 1716 (C=O), 1330, 1161 (SO_2-N); δ_H (250 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.5, CH*Me*), 1.95 (2H, m, C*H*$_2$CHOBz), 2.24 (3H, s, *Me*-aryl), 2.24 (2H, m, C*H*$_2$CO), 3.54-3.67 (1H, br.m, C*H*Me), 3.97 (2H, s, C*H*$_2$OBn), 4.50 (2H, s, C*H*$_2$Ph), 4.75 (1H, d, *J* 9.0, N*H*), 5.03 (1H, m, C*H*OBz) and 7.16-7.93 (14H, m, *Ph* and *aryl*); δ_C (62.9 MHz, $CDCl_3$) 18.9 (CH_3, CH*Me*), 21.4 (CH_3, *Me*-aryl), 24.6 (CH_2, *C*H_2CHOBz), 34.4 (CH_2, *C*H_2CO), 52.3 (CH, *C*HMe), 73.2, 74.8 (2xCH_2, *C*H_2Ph and *C*H_2OBn), 75.6 (CH, *C*HOBz), 126.8, 127.8, 128.4, 129.6, 133.3 (CH, *Ph* and *aryl*), 127.8, 137.0, 137.7, 143.3 (C, *Ph* and *aryl*), 166.1 (C, *C*=O benzoate) and 207.4 (C, *C*=O ketone); *m/z* (C.I.) 527 [$(M+NH_4)^+$], 509.

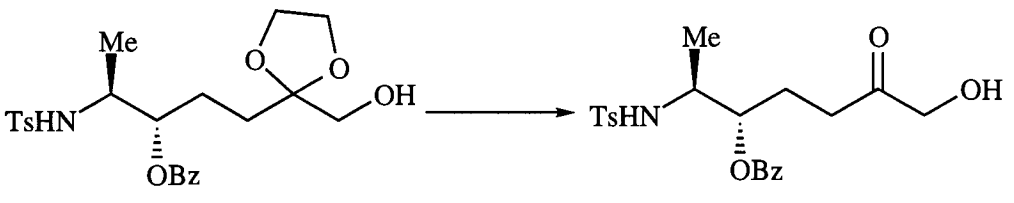
5.3.25 (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-6,6-ethylenedi oxyheptan-7-ol ***141***



128 **141**

To the α,β-acetylenic ketal **128** (44 mg, 0.08 mmol) in ethanol (2 ml) was added palladium (10% on C, 35 mg) and the mixture stirred under an atmosphere of hydrogen for 20 hours. The catalyst was removed by filtration through a plug of Celite, washed with DCM (2 x 2 ml) and the combined filtrates concentrated *in vacuo*. The residue was subjected to column chromatography eluting with EtOAc-hexane (2:1) to give the *saturated ketal* **141** (19 mg, 51%). R_F 0.48; υ_{max}/cm^{-1} (film, IR card) 3272br (OH), 1716 (C=O), 1329, 1159 (SO_2-N), 1273, 1092 (C-O); δ_H (250 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.5, CH*Me*), 1.60-1.95 (5H, m, CHCH_2CH_2 and CHO*H*), 2.34 (3H, s, *Me*-aryl), 3.43 (2H, br.s, CH_2OH), 3.52-3.71 (1H, m, C*H*Me), 3.91-4.12 (4H, m, CH_2CH_2), 4.90 (1H, br.d, *J* 8.5, N*H*), 5.05 (1H, m, C*H*OBz), 7.16-7.95 (9H, m, *Ph* and *aryl*); δ_C (62.9 MHz, $CDCl_3$) 18.9 (CH_3, CH*Me*), 21.3 (CH_3, *Me*-aryl), 24.9, 30.0 (2xCH_2, CHCH_2CH_2), 52.1 (CH, *C*HMe), 65.3, 65.4 (2xCH_2, CH_2CH_2 and CH_2OH), 77.1 (CH, *C*HOBz), 109.6 (C, *C*-ketal), 126.7, 126.8, 128.2, 129.5, 129.6, 133.1 (CH, *Ph* and *aryl*), 129.5, 137.8, 143.2 (C, *Ph* and *aryl*) and 166.1 (C, *C*=O); *m/z* (C.I.) 481 [$(M+NH_4)^+$], 198, 105; [Found: $(M+NH_4)^+$, 481.20080. $C_{23}H_{33}N_2O_7S$ requires $(M+NH_4)$, 481.20085].

5.3.26 (2S, 3S)-N-(4-methylphenylsulfonyl)-2-amino-3-benzoyloxy-6-oxoheptan-7-ol ***142***



141 **142**

A stirred solution of the ketal **141** (17 mg, 0.04 mmol) in DCM (2 ml) was treated with montmorrillonite K10 (100 mg) and the mixture was heated under reflux for 24 hours. The cooled mixture was filtered through a plug of Celite to remove the clay and the Celite washed with DCM (2 x 2 ml). The combined organic extracts were concentrated *in vacuo* and subjected to column chromatography eluting with EtOAc-hexane (2:1) to yield a oily residue (5 mg, 29%).

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